# VA Northeast Ohio Healthcare System

# Human Research Protection Program Standard Operating Procedures

**Version .09**

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**Chapter 1 Human Research Protection Program (HRPP)**

## 1.1 Purpose

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VA Northeast Ohio Healthcare System (VANEOHS) Medical Center fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In the review and conduct of research, actions by the Organization will be guided by the principles (i.e., respect for persons, beneficence, and justice) set forth in the ***Ethical Principles and Guidelines for the Protection of Human Subjects of Research*** (often referred to as the Belmont Report). The actions of VANEOHS will also conform to all applicable VA, federal, state, and local laws and regulations. In order to fulfill this policy, the Organization has established a human research protection program (HRPP).

## 1.2 Mission:

The Veteran's Health Administration (VHA) Mission Statement: Honor America's veterans by providing exceptional health care that improves their health and well-being.

The VHA Vision Statement: To be a patient-centered integrated health care organization for veterans providing excellent health care, research, and education; an organization where people choose to work; an active community partner; and a back-up for National emergencies

One of the VHA Strategies is to focus research and development on clinical and system improvements designed to enhance the health and well-being of veterans.

VANEOHS is authorized to care for veterans and to conduct research that supports the mission of the VHA and enhances the quality of health care delivery to veterans.

The mission of the VANEOHS Human Research Protection Program (HRPP) is:

- To safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- To provide timely and high quality education, review, and monitoring of human research projects; and
- To facilitate excellence in human subjects research. The HRPP is a multi-tiered program. :

## 1.3 Institutional Authority

The HRPP operates under the authority of the medical center policy 151- 018 "Human Research Protection Program (HRPP)" adopted on September 1, 2004. As stated in that

policy, the operating procedures in this document "...serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the VANEOHS." The HRPP Policy and these operating procedures are made available to all investigators and study staff and are posted on the Intranet/ internet website (http://www.clevelandvaresearch.org) and copies are available upon request.

## 1.4 Definitions

**Research.** Research as defined by VA regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge (38 CFR 16.102(d)).
For the purposes of this policy, a **"systematic investigation"** is an activity that involves a prospective study plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

**Human Subject**. A human subject as defined by VA regulations means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) information or biospecimens through intervention or interaction with the individual and uses, studies, or analyzes the information or biospecimens; or (2) Obtains, uses, studies, analyzes or generates identifiable private information or biospecimens.

- Intervention as defined by VA regulations means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Interaction as defined by VA regulations means communication or interpersonal contact between investigator and subject.
- Private information as defined by VA regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public
- Identifiable private information as defined by VA means information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimens.
- Identifiable biospecimen as defined by VA means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen

For research covered by Food and Drug Administration (FDA) regulations, human subject means an individual who is or becomes a participant in a clinical investigation (as defined below), either as a recipient of the test article or as a control. A subject may be in normal health or may have a medical condition or disease. In research involving

devices, a human subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control.

Note: The terms “subject” and “participant” are used interchangeably in this document and have the same definition.

Research as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]
- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]”

**Test Article.** Test articles covered under the FDA regulations include:

a. **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary: A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; A substance (other than food) intended to affect the structure or any function of the body; A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

b. **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other

animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
*http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm*

c. **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
*http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm*

d. **Food Additives** - In its broadest sense, a food additive is any substance added to food. Legally, the term refers to "any substance the intended use of which results or may reasonably be expected to result -- directly or indirectly -- in its becoming a component or otherwise affecting the characteristics of any food." This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food.

***e.*** **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color.
*http://www.fda.gov/Food/FoodIngredientsPackaging/ucm094211.htm#foodadd*

**f. Foods**, including dietary supplements that bear a nutrient content claim or a health claim

**g. Infant formulas**

**Institutional Review Board (IRB).** An IRB is a board, committee, or other group formally designated by an institution to review, approve, require modification in, disapprove, and conduct continuing oversight of human research in accordance with 38 CFR Part 16 and other applicable VA and Federal requirements. The IRB is a subcommittee of the R&D Committee.

**Institutional Official (IO).** The IO is the medical center Director. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance.

**Principal Investigator (PI).** A PI is an individual who conducts a research investigation, i.e., under whose immediate direction research is conducted, or, in the

event of an investigation conducted by a team of individuals, is the responsible leader of that team. FDA considers PI and investigator as being the same. The PI oversees scientific, technical, and day-to-day management of the research.

**Co-Investigator (Co-I).** A Co-I is an individual who, under the direction of the PI, is involved in some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of identifiable data, and writing of manuscripts resulting from the project. The investigator must uphold professional and ethical standards and practices, adhere to all applicable Federal requirements, and comply with applicable local policies and procedures

**Research under the Auspices of the VANEOHS** is research that is conducted by VANEOHS investigators (serving on VA compensated, WOC, or IPA appointments) while on VA time or on VA property. The research may be funded by VA, by other sponsors, or be unfunded. VA research must have R&D Committee approval before it is considered VA Research and before it can be initiated. All research activities approved by the R&D Committee are considered VA Research.

## 1.5 Ethical Principles

VANEOHS is committed to conducting research with the highest regard for the welfare of human subjects. It upholds and adheres to the principles of *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research* by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (1979). These principles are:

1. **Respect for Persons**, which is ensured by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
2. **Beneficence**, which is assured by ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
3. **Justice,** the equitable selection of subjects.

The HRPP of VANEOHS, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

## 1.6 Regulatory Compliance

The HRPP is responsible for ensuring compliance with federal regulations, state law, and the policies of the Department of Veterans Affairs. All human subjects research at the VANEOHS is conducted in accordance with the policy and regulations found in applicable handbooks including but not limited to VHA Handbook 1200.01, VHA Handbook 1200.05, 38 CFR 16, 45 CFR 46 and 21 CFR 50 and 56. The actions of the VANEOHS also conform to all other applicable federal, state, and local laws and regulations.

## 1.7 Federalwide Assurance (FWA)

The HRPP operates under the authority of its current Federalwide Assurance (FWA00004231) and has designated the IRB's noted below to review all human research protocols.

IRB00000971 Advarra, Inc. IRB#1

IRB00000781 National Cancer Institute Central IRB #1 (Adult)

IRB00009430 National Cancer Institute Central IRB #3

IRB00010018 National Cancer Institute Central IRB #4

IRB00000686 VA Northeast Ohio Healthcare System IRB

IRB00006332 Veterans Hlth Administration Central Ofc IRB #1

IRB00012307 Veterans Hlth Administration Central Ofc IRB #1

IRB00000533 WCG IRB

## 1.8 Activities Covered by the HRPP

The HRPP of the VANEOHS covers all research involving human subjects that is conducted completely or partially in facilities of the Northeast Ohio Healthcare System, conducted in approved off-site locations, facilities, and/or conducted by researchers of the VANEOHS, employees, or agents, while on official VA duty time. It includes research conducted using non-public patient data from VA records, using VA resources, publishing or presenting results with the VA cited as supporting or conducting the research, or recruiting VA patients at VA facilities. The research may be VA funded, funded from non-VA sources, or conducted without direct funding.

## 1.9 Types of Research Typically Covered by the HRPP

Research conducted at the VANEOHS is generally designed to advance health care for our veteran population and the nation. The HRPP typically covers the following types of research: Biomedical, Behavioral, Psychological, Sponsored Research, and Health Services Research.

## 1.10 Categories of Participants Typically Covered By The HRPP

Research subjects are generally veterans receiving health care from the VA, care givers, healthy volunteers and those with conditions that affect the veteran population. Typical research subjects are adults with independent decision-making capacity.

## 1.11 Written Policies and Procedures

Medical center policy 151-018 “Human Research Protection Program” and this SOP detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the VA Northeast Ohio Healthcare System R&D Committee and IRB.

The policies and procedures present the most current information for reference by potential investigators and their staff. This is not however, a static document. The policies and procedures are reviewed for adequacy by the R&D Committee. Revisions to the SOPs are reviewed, and approved by the IRB, and final approval is given by the R&D Committee. The ACOS/R&D will keep the research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website and through the VA electronic mailing system. The policies and procedures will be available on the website (http://www.clevelandvaresearch.org), and copies available upon request.

## 1.12 HRPP Organization

The HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The HRPP is a multi-tiered program involving the following:

- Medical Center Director
- Chief of Staff (COS)
- Deputy Medical Center Director
- Associate Medical Center Director
- Associate Director of Patient Care Services
- Research Service
    - Associate Chief of Staff for Research and Development (ACOS/R&D)
    - Administrative Officer for Research and Development (AO/R&D)
    - Research and Development (R&D) Committee
        - R&D Committee Coordinator (R&DC)
    - Institutional Review Board (IRB)
        - IRB Administrator and Staff
    - Subcommittee on Research Safety (SRS)
        - Research Safety Coordinator/Chemical Hygiene Officer (RSC)
    - Conflict of Interest (COI) Administrator and Committee
    - Research Credentialing Coordinator (RCC)

- Executive Director, Staff, and Board of Directors of the Cleveland VA Medical Research and Education Foundation (Foundation)
- Investigators
- Study Staff
- Research Subject/Participant

- Other Medical Center Services, Committees and/or Employees
  - Medical Executive Committee (MEC)
  - Nursing Service and Nursing Research Council
  - Pharmacy Service
  - Pharmacy & Therapeutics (P&T) Committee
  - Environment of Care (EOC) Committee
  - Radiation Safety Committee
    - Radiation Safety Officer (RSO)
  - Information System Security Officer (ISSO)
  - Risk Management and the Patient Advocates
  - Patient Care Administrative Staff (PCAS)
    - Privacy Officer (PO)
  - Research Compliance Office
    - Research Compliance Officer (RCO)
    - Research Compliance Auditor (RCA)
  - Regional Counsel's Office
- Other Institutions and Committees
  - Case Western Reserve University (Case) and IRB Advisory Committee (IAC)
  - Case Conflict of Interests Committee (CCOI)
  - Case Institutional Biosafety Committee (IBC)

The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units, and individuals have primary and secondary responsibilities for implementing the HRPP:

### 1.13.1 Institutional Responsibilities

It is the responsibility of the VANEOHS to formally assure the VA and other Federal agencies in writing that it will comply with regulations governing the protection of human subjects. As part of the written FWA to the government, SOPs have been developed for conducting human subject research in a responsible and ethical fashion.

### 1.13.2 Medical Center Director

VA policy at VHA Handbook 1200.05 requires that the medical center Director serve as the IO for the VANEOHS's FWA. Consequently, the medical center Director is fully responsible for overseeing the protection of human subjects within the VANEOHS, including:

1. Fostering an institutional culture supporting ethical conduct of all research involving human subjects.
2. Serving as the signatory authority.
3. Overseeing the R&D Committee, IRB, and other applicable subcommittees of the R&D Committee, facility research office, and all VA investigators and VA research staff who conduct human subjects research at that facility
4. Completing assurance training prior to signing the FWA and every three years after that.
5. Appointing a Research Compliance Officer, who is responsible for implementing a research compliance program.
6. Maintaining open channels of communication among all parties involved in the human subject protection process.
7. Ensuring that the VANEOHS IRB and HRPP is provided with sufficient meeting space and staff to support its substantial review and record-keeping responsibilities.
8. Ensuring that a procedure is in place to review and approve recruiting documents, flyers, and advertisements for research that is not VA research prior to being posted or distributed in any form within or on the premises of a VA facility.
7. Ensuring notification of ORO, OHRP, FDA, and ORD of (1) any unanticipated problem involving risks to subjects or others; (2) any serious or continuing noncompliance with IRB requirements by research investigators; or (3) any for-cause suspension or termination of IRB approval, in accordance with applicable Federal regulations. Such notice will be accomplished in coordination with the ACOS/R&D, R&D Committee Chairperson, IRB Co-Chairperson, and RCO.
8. Overseeing implementation of a research compliance monitoring process that provides monitoring reports, as appropriate, to the IO, ACOS/R&D, RCO, R&D

Committee Chairperson, and IRB Co-Chairperson.
9. Submitting, implementing, and maintaining an approved FWA through the VISN Network Director, ORO, and the DHHS OHRP.
10. Appointing Committee members, and Chairpersons and Vice-Chairperson(s) for both the R&D Committee and IRB upon recommendation from the applicable committee.
11. Reviewing and approving or disapproving any request for permission to conduct international research.
13. Signing and adhering to the Memorandum of Understanding (MOU) for use of the VA Central IRB and other IRBs as applicable.
14. Delegating authority to an individual to comment and respond to VA Central IRB review.
15. Delegating authority to an individual to serve as liaison between the facility and both the Local Site Investigator and the VA Central IRB.
16. Is available to all IRB Members.

The medical center Director delegates the responsibility for the VANEOHS R&D program to the ACOS/R&D, who is advised and assisted by the R&D Committee.

**1.13.3 Chief of Staff (COS)**
The Chief of Staff (COS) has overall responsibility for all clinical activities under the purview of the VANEOHS. The COS provides guidance and is the direct supervisor of the ACOS/R&D. He/she reviews problems and issues related to human subjects research that is brought to his/her attention by the ACOS/R&D and others. COS serves as ex-officio member of the R&D Committee. The COS will apprise the medical center Director of issues of significance.

**1.13.4 Deputy Medical Center Director**

The Deputy Medical Center Director is responsible for assigned administrative services of the medical center.

**1.13.5 Associate Medical Center Director**
The Associate Medical Center Director is responsible for assigned administrative services of the medical center

**1.13.6 Associate Director Patient Care Services**

The Associate Director Patient Care Services is responsible for all nursing research activities.

**1.13.7 Research Service**

1.13.7.1 Associate Chief of Staff for Research and Development (ACOS/R&D)

The ACOS/R&D is delegated responsibility for the daily management of the VANEOHS's R&D program, including the operations of the IRB. The ACOS/R&D reports to the

medical center Director through the COS and is responsible for:

1. Implementing the institutions HRPP policy.
2. Ensuring that the administrative structure is in place and functioning effectively to carry out the research mission of the medical center and in compliance with the regulations.
3. Acting as liaison between VHA ORD and the R&D Committee, as well as advising the Director on key matters regarding research at the VANEOHS.
4. Administering the R&D Program, including the R&D Committee and its subcommittees.
5. Overseeing the financial management of the VANEOHS's R&D Program.
6. Assisting investigators in their efforts to carry out VA's research mission.
7. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
8. Assuring accurate, up-to-date records regarding mandatory training and certification of R&D members, IRB members, investigators, and study staff in the protection of human subjects in research are maintained.
9. Serving as executive secretary of the R&D committee.

The Office of the ACOS/R&D is responsible for informing and instructing all eligible VA employees of the policies and procedures for obtaining approval to conduct research.

### 1.13.7.2 Administrative Officer for Research and Development (AO/R&D)

The AO/R&D supervises the day-to-day operations of the Research Office and provides staff support to the R&D Committee and IRB. The AO/R&D is expected to be knowledgeable of Federal-wide requirements provided in both regulations and interpretations for conducting human studies research and to use this knowledge to advise the ACOS/R&D, the R&D Committee, and investigators concerning relevant issues. The AO/R&D is responsible for ensuring that a) R&D Committee meetings are scheduled, b) review materials are complete and distributed prior to the meetings for review, c) minutes are recorded accurately, d) decisions are communicated to investigators in a reasonable time, e) reports are obtained and generated on time, and f) records are maintained.

### 1.13.7.3 Research and Development (R&D) Committee

The VANEOHS R&D Committee provides overall direction and oversight of the VANEOHS R&D Program and is responsible for maintaining high scientific standards throughout the program. These include ensuring the scientific and ethical quality of VA research projects, the protection of human subjects in research, the safety of personnel engaged in research, the welfare of laboratory animals, security of VA data, and the security of VHA research laboratories. The R&D Committee plays a crucial role in the establishment and development of the HRPP (See medical center policy 151-001 "Research and Development Committee" for a more detailed description of the R&D

Committee).

All proposed research involving human subjects must be reviewed and approved by both the R&D Committee and the IRB, unless exempt from IRB review.

The R&D Committee is responsible for:

1. Providing oversight of the HRPP
2. Assuring a scientific review of all research projects conducted at the VANEOHS. It evaluates the quality, design, desirability, propriety, administrative feasibility, and relevance to and in support of the VHA's mission of all research proposals (funded or non-funded) and applications for grants and research awards.
3. Maintaining high standards for the quality of the research, ensuring the scientific merit, the protection of human subjects (including privacy and confidentiality), and the implementation of adequate safety measures for research subjects and study staff.

Any issues regarding the HRPP are brought forward to the R&D Committee as a formal agenda item. Policy to protect the human research subjects reviewed and approved by the R&D Committee and IRB and implemented as appropriate by the subcommittees, the R&D Service administrative staff, investigators, and employees of the VANEOHS.

#### 1.13.7.3.1 R&D Committee Coordinator

The R&D Committee Coordinator is responsible for providing administrative and clerical support to the R&D Committee, as well as the scheduling and coordination of the activities of the R&D Committee. He/she ensures that each study receives all appropriate reviews and approvals prior to providing final R&D Committee approval to the investigator.

### 1.13.7.4 Institutional Review Board (IRB)

The VANEOHS's IRB is appointed by the medical center Director, acting as a subcommittee of the R&D Committee. The IRB prospectively reviews and makes decisions concerning all human research conducted at its facilities or by its employees or agents, or under its auspices. The IRB is responsible for the protection of rights and welfare of human research subjects at the VANEOHS. It discharges this duty by complying with the requirements of the Common Rule; FDA regulations; the FWA and the VHA Handbooks 1200 series.

#### 1.13.7.4.1 IRB Administrator and Staff

The IRB Administrator and Staff are responsible for ensuring that: a) IRB meetings are scheduled, b) review materials are complete and distributed for review prior to the meetings, c) decisions are communicated to investigators in a reasonable time, d) minutes are recorded accurately, e) reports are obtained and generated on time, and f) records are maintained. Additionally, the IRB Administrator and Staff advise and educate

investigators and study staff regarding operational procedures for obtaining and maintaining approval to conduct research. The IRB Administrator oversees the preparation of the agenda, review materials, records the minutes, prepares communications to the investigators. The IRB Administrator has a number of other responsibilities that include, but are not limited to: reporting changes in IRB membership to OHRP and ORO; facilitating communication between the investigators and the IRB; maintaining quality control of IRB support functions; ensuring that documentation of IRB activities and decisions satisfies all regulatory requirements; and assisting in any regulatory site visits.

### 1.13.7.5 Subcommittee on Research Safety (SRS)

The SRS is a subcommittee of the R&D Committee. It is the research organizational unit charged with the responsibility for reviewing all research activities, which involve the following: biological hazards (microbiological or viral agents, pathogens, toxins, or select agents), human and non-human cells or tissue samples, Recombinant or Synthetic Nucleic Acid Molecules, OSHA and EPA deemed hazardous chemicals, controlled substances (narcotics), and radiation hazards. It reviews and acts upon all active research protocols annually, and provides written notification to the R&D Committee Coordinator when approved.

#### 1.13.7.5.1 Research Safety Coordinator/Chemical Hygiene Officer (RSC)

The RSC coordinates all safety activities in the research laboratories by ensuring coordination with other regulatory programs, personnel, or committees, such as the Radiation Safety Officer and/or Radiation Safety Committee and the Chemical Hygiene Committee and/or the Facility Safety Office. The RSC reviews, prepares, and records information for the SRS. The RSC ensures that a complete list of all products that contain chemical designation or identified by Occupational Safety and Health Administration and/or the Environmental Protection Agency as hazardous have been submitted to him/her for review and approval prior to being purchased. The RSC also coordinates all safety-related activities in research laboratories including: mandatory safety training, safety inspections, reporting accidents, and acting as a liaison for activities with all facility security and safety committees and officials. Additionally, the RSC assures that all laboratory personnel receive annual training specific to research activities, and evaluates, on an annual basis, the effectiveness of the laboratory's Chemical Hygiene Plan.

### 1.13.7.6 Conflict of Interest (COI) Administrator

The **COI Administrator** is responsible for conducting the review process, including initial review and at Continuing Review of the disclosure forms prior to the R&D Committee and IRB review and determines whether a referral to General Counsel is deemed as necessary. He/she serves as staff for the review process; and maintains records and

official files for the COI process. The ACOS/R&D and/or AO/R&D may serve as the COI Administrator. The ACOS/R&D and AO/R&D are members of the Case Conflict of Interest Committee representing the VANEOHS.

### 1.13.7.7 Research Credentialing Coordinator (RCC)

The RCC manages and coordinates a system of research credentialing, the purpose of which is to protect human subjects by confirming that study staff are fully qualified to conduct the research duties that they are assigned. This responsibility involves coordinating the credentialing effort with investigators, Human Resource Management Service, the Medical Staff Office and the ACOS for Education, if necessary. The RCC is responsible for obtaining information from investigators on all new staff and ensuring that investigators are informed when staff has been fully cleared by the credentialing process to begin work in human studies research. The RCC also ensures the maintenance of electronic copy folders with credentialing information for all human studies investigators and staff.

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### 1.13.7.8 The Executive Director, Staff and Board of Directors of the Cleveland VA Medical Research and Education Foundation (Foundation)

The Foundation is a VA non-profit foundation established pursuant to PL 100-322 and 38 USC 7361-7368, et seq. It provides a flexible funding mechanism and, as such, facilitates approved sponsored research at the VANEOHS. The Foundation facilitates the conduct of the studies which have been approved by the R&D Committee and uses all reasonable efforts to ensure performance of Cooperative Research and Development Agreement (CRADA)/ agreements).

The Foundation Executive Director works in concert with all of the components of the HRPP to ensure that research supported by this organization is carried out with the utmost protections in place for human subjects. The Executive Director enhances the the VANEOHS's HRPP by ensuring funds are made available to the medical center to assist in its efforts regarding training, education, credentialing, compliance and accreditation. These funds are distributed in accordance with VHA policy. The Foundation also facilitates the distribution of research awards from itself.

The Foundation maintains FWA00004354.

### 1.13.7.9 The Investigator

The investigator is the ultimate protector of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards and for developing a protocol that incorporates the principles of the Belmont Report. He/she is expected to conduct research in accordance with the approved research protocol and to oversee all aspects of the research by providing supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent and

the investigator must establish and maintain an open line of communication with all research subjects within his/her responsibility. In addition to complying with all the policies and standards of the governing regulatory bodies, the investigator must comply with institutional and administrative requirements for conducting research. The investigator is responsible for ensuring that all study staff complete appropriate training and must obtain all required approvals prior to initiating research. See Section 10 for a detailed description of Investigator Responsibilities.

#### 1.13.7.10 Study Staff

Every member of the study staff is responsible for protecting human subjects. Study coordinators, nurses, research assistants, and all other study staff have a strict obligation to comply with all IRB determinations and procedures; adhere rigorously to all protocol requirements; inform investigators of all adverse events, unanticipated problems, or protocol deviations involving risks to subjects or others; oversee the adequacy of the informed consent process; and take whatever measures are necessary to protect the safety and welfare of subjects.

Researchers/staff involved in research at every level are responsible for notifying the IRB promptly of any noncompliance with applicable regulatory requirements, and/or determinations of the IRB **and/or failure to follow VA requirements** of which they become aware, whether or not they themselves are involved in the research. Researchers/staff may also notify the RCO directly of any compliance concerns they may have.

#### 1.13.7.11 Research Subjects/Participants

Subjects may be viewed as having certain responsibilities as well. They can be expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation. While participating, they should also make every reasonable effort to comply with protocol requirements and inform the investigators of unanticipated problems. Subjects always have the right to withdraw from their participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.

### 1.13.8 Other Medical Center Services, Committees, and/or Employees

#### 1.13.8.1 Medical Executive Committee (MEC)

The MEC meets monthly and serves as the executive committee of the medical staff of the VANEOHS. The MEC receives, acts on, and approves criteria for granting clinical privileges for each clinical service and makes recommendations directly to the medical center Director regarding the structure, operations, personnel management, ethics, and self governance of the Medical Staff.

The MEC reviews and evaluates: a) the quality of clinical programs and the clinical performance of Medical Staff members; b) risk management activities, c) the scope, quality, and effectiveness of medical educational programs at the VANEOHS, d) the professional development of the Medical Staff members, and e) the scope, quality, and productivity of research programs at the VANEOHS.

The MEC reviews the final R&D Minutes. The ACOS/R&D also reports regularly to the MEC and keeps the MEC informed on research related activities and the HRPP.

### 1.13.8.2 Nursing Service and Nursing Research Council

The nursing staff at the VANEOHS provides state-of-the-art, cost-effective nursing care to patients and families as they respond to health and illness. Nursing staff may be involved in research as the research investigator or as part of their ordinary clinical activities. They are expected to exercise independent judgment in the protection of the rights and welfare of their patients. If there are any concerns about research practices, staff are urged to contact the Associate Chief Nurse for Research and/or the PI immediately. If staff are not comfortable with contacting the PI or the study staff, then the ACOS/R&D, AO/R&D or the IRB Administrator should be contacted immediately.

The purpose of the Nursing Research Council is to promote an environment in which evidenced based practice and research is utilized to enhance patient care, nursing outcomes and professional practice. The Chair of the Nursing Research Council is encouraged to become a member of the R&D Committee.

### 1.13.8.3 Pharmacy Service

Pharmacy Service at the VANEOHS assumes responsibility for implementing FDA regulations concerning investigational drugs. The Pharmacy receives all drugs used in research at the VANEOHS, maintains records accounting for the use of the drugs, monitors investigators' compliance with local and FDA requirements, dispenses study drugs and disposes of them at the end of the study.

#### 1.13.8.3.1 Pharmacy and Therapeutics (P&T) Committee

The P&T Committee serves in an advisory capacity to the MEC on policies pertaining to appropriate use of drugs. They evaluate information on all drugs proposed for use in the medical center and Outpatient Clinics, and establish guidelines or criteria for use where necessary. They authorize use of drugs for other than FDA approved indications, and approve investigational use of drugs, in conjunction with the IRB, to assure patient safety and appropriate quality controls in storage, preparation, and dispensing by Pharmacy Service.

### 1.13.8.4 Environment of Care (EOC) Committee

One of the duties of the EOC Committee is to analyze any electrically line-operated

devices that are not used for their standard application or if the device is specially constructed by research staff. The EOC submits recommendations for action to the PI. The EOC collaborates with responsible staff, services, or product lines to implement recommendations, track items/issues to resolution, and monitor effectiveness of actions taken. Consultation and technical assistance are provided as needed.

#### 1.13.8.5 Radiation Safety Committee

The Radiation Safety Committee oversees the use of all medical center ionizing radiation sources to ensure safe, responsible practices and full compliance with Radiation Safety Program requirements. The Radiation Safety Committee reviews and approves or disapproves as appropriate all research protocols that involve the use of ionizing radiation. It is responsible for ensuring the safe use of all forms of ionizing radiation per applicable regulations from the Nuclear Regulatory Commission, the State of Ohio, the Department of Transportation, the FDA, Environmental Protection Agency, the Joint Commission, and the Department of Veterans Affairs.

##### 1.13.8.5.1 Radiation Safety Officer (RSO)

The RSO administers, coordinates, and manages the Radiation Safety Management Program and Radiation Safety Program activities. The RSO serves as the liaison between the Radiation Safety Committee (RSC), the IRB, the SRS, and the EOC. The RSO keeps the RSC informed of any ionizing radiation safety issues.

#### 1.13.8.6 Information System Security Officer (ISSO)

The ISSO's serves in an advisory capacity to the IRB and the R&DC, responsibilities related to the HRPP include:

- Providing guidance and assistance to the Research Office, IRB Office, investigators, and study staff related to research data information security.
- Reviewing and, when appropriate, approving PIs' requests for storing VA research data outside the VA.
- Serving as a member of the Pre-review Team in review of human studies applications.
- Reviewing proposed study protocols and any other relevant materials submitted with the IRB application.
- Identifying deficiencies and making recommendations to the investigator of options available to correct the deficiencies
- Providing summary reports on each study within a time frame that does not prolong the study approval process.
- The ISSO is responsible for ensuring that the proposed research complies with information security requirements for VA sensitive information.

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### 1.13.8.7 Risk Management and the Patient Advocates

Patient advocates, located within Risk Management at the VANEOHS, assist with the intake of complaints from research subjects and the investigations related to a research complaint. When necessary, they are also charged with supporting an Administrative Board of Investigations should an allegation of Research Misconduct arise.

### 1.13.8.8 Patient Care and Administrative Staff (PCAS)

PCAS at the VANEOHS work in concert with the facility Compliance Officer to ensure that billing for research services are properly and adequately handled in accordance with institutional requirements and federal regulations.

### 1.13.8.9 Privacy Officer (PO)

The Privacy Officer is the authoritative source for privacy within the VANEOHS. The PO serves in an advisory capacity to the IRB and R&DC. The PO's responsibilities related to the HRPP are:

- Ensuring the facility's overall compliance with privacy policies and requirements
- Reporting incidents regarding protected health information (PHI) to the Privacy Violation Tracking System and participating in the investigation of such incidents
- Ensuring all employees are trained on privacy annually
- Serving as a consultant to the IRB and R&DC.
- Serving as a member of the Pre-review Team in review of human studies applications,
- Reviewing proposed study protocol and any other relevant materials submitted with the IRB application
- Identifying deficiencies and making recommendations to the investigator of options available to correct the deficiencies
- Ensure that the required language for a valid authorization to release protected health information for human subjects research purposes is part of the protocol if applicable and that the Informe Consent Document (ICD) and HIPAA document are consistent.
- Providing summary reports on each within a time frame that does not prolong the study approval process.
- The PO is responsible for ensuring that the proposed research complies with VA Privacy requirements and the HIPAA Authorization contains all required elements.

### 1.13.8.10 Research Compliance Office

The Research Compliance Office consists of the Research Compliance Officer (RCO) and Research Compliance Auditor (RCA)

An RCO's primary responsibility is auditing and reviewing research projects relative to requirements for the protection of human subjects, laboratory animal welfare, research safety, and other areas under the jurisdiction of and specified by the ORO.

In addition to conducting required audits, the RCO may serve as a nonvoting consultant, as needed, to the facility's R&D Committee, IRB, and other research review committees. The RCO may attend meetings of these committees when requested by the committee.

### 1.13.8.11 Regional Counsel's Office

The HRPP, the R&D Committee, and the IRB rely on the VA Regional Counsel's Office for the interpretations and applications of VA regulations, Ohio law, and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The Regional Counsel may also assist in making determinations regarding conflict of interest.

## 1.13.9 Other Institutions and Committees

### 1.13.9.1 Case Western Reserve University (Case) and the Institutional Review Board Advisory Committee (IAC)

Case is the VANEOHS's affiliate university. It administers research funding for non-VA federal sources. As stipulated by federal regulations, it is the responsibility of Case, the grantee, to oversee all of its ongoing research. In light of this cognition, an Institutional Review Board Advisory Committee (IAC) was formed among Case and its affiliated institutions, namely the VANEOHS, MetroHealth Medical Center, University Hospitals Case Medical Center, and the Cleveland Clinic Foundation. This relationship encourages and enhances the protection of human subjects across neighboring facilities. In addition to the IAC, the VANEOHS works very closely with Case's Research Compliance Office to ensure conflict of interests are disclosed properly and adequately, and that other preventative steps are taken to ensure the protection of human subjects.

The IRB Co-Chairperson and the IRB Administrator are voting members of the IAC. The IRB Office Staff serve as alternate for the Administrator. This committee provides a means for information sharing and discussion related to human subjects research. In addition, the IAC provides an IRB Member Symposium which is open to all IRB members from the affiliated institutions and provides an educational session related to human subject protections. Case also provides a Continuing Research Education

Program that is open to all of its affiliates.

*Please note that the Northeast Ohio Healthcare system IRB does not serve as the IRB of record for any of the above named academic affiliates.*

### 1.13.9.2 Case Institutional Biosafety Committee (IBC)

The Case Western Reserve University (CWRU) Institutional Biosafety Committee (IBC) reviews, approves, and oversees projects involving Recombinant or Synthetic Nucleic Acid Molecules in accordance with the National Institutes of Health (NIH) Guidelines. The VANEOHS has an MOU with CWRU to utilize their IBC in the event that such research is conducted under the auspices of the VANEOHS.

The VANEOHS relies on the review of the CWRU IBC. As per the Memorandum of Understanding (MOU) with CWRU, the VA SRS Chairperson (or Alternate Chairperson) attends the CWRU IBC meetings each month, as they serve as voting members on the IBC. This mechanism allows the VANEOHS to be in compliance with NIH and VHA Handbook 1200.08 “Safety of Personnel Engaged in Research”. In addition, this process provides coordinated review and communications between the CWRU IBC, the SRS, the IRB, the PI, and the R&D Committee.

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### 1.13.9.3 Case Conflict of Interests Committee (COI)

The Case Conflict of Interests Committee (COI) is composed of Case faculty, Case university representatives from Research Administration, Technology Transfer, and Finance and Administration, IRB, and compliance representatives from Case’s affiliated hospitals. The Case Offices of General Counsel and Internal Audit participate in an advisory, non-voting capacity, as well.

The primary duties of the COI include the ongoing development of conflict of interest policy and procedures for Case, coordination of these policies and procedures with the affiliate/partner hospitals, review of conflict of interest disclosures submitted by Case Faculty and investigators on sponsored research, and the development of conflict of interest management plans, in consultation with Case Deans and Department chairs, as necessary.

The ACOS/R&D and AO/R&D, of the VANEOHS are voting members of the Case Conflict of Interests Committee. The AO/R&D serves as an alternate for the ACOS/R&D. This forum allows for a coordinated review of potential investigator conflicts among the Case affiliated institutions and provides a means of sharing investigator management plans with the affected affiliate.

## 1.14 Relationship among Components (See Organizational Chart)

The interaction and relationships among the HRPP components is a continuous and evolving process and occurs routinely and on multiple levels and is managed through a number of mechanisms, including convened standing committee meetings, overlapping membership on local committees, and informal associations among individuals that are part of the HRPP.

### Interaction within the Research Service

Periodic “Research Service Staff Meetings” are held to discuss the ongoing initiatives of the R&D program. This forum allows for an exchange of information from the various individuals and committee representatives involved in the HRPP (ACOS/R&D, AO/R&D, Research Administrative Staff, IRB Staff, RCO, RSC, RIRM, RCC, R&D Committee Coordinator, and the Foundation Executive Director).

### Interaction between the Research Service and the rest of HRPP

The R&DC Coordinator and IRB Staff interact routinely and regularly with the IRB/R&D Committee Chairpersons/Vice-Chairperson(s) and Chairperson of the SRS as needed: a) prior to the respective committee meetings to prepare and review the agenda, b) during the meeting while the review process is ongoing, and c) after the meeting for the generation of decision letters.

The R&D Committee Coordinator, ISSO, PO, and a member(s) of the IRB Administrative Staff comprise the Pre-review Team who provides a preliminary review of new research protocols to determine if all necessary requirements for submission have been fulfilled. The R&DCC or IRB Administrator or staff may consult other members of the HRPP (IRB Co-Chairperson, R&D Chairperson, RSC, Executive Director of the Foundation, etc.) as deemed necessary

Communication and interaction with the Pharmacy Service is provided by a Pharmacy Representative serving as a voting member of the IRB, and a Pharmacy Representative serving as a voting member of the R&D Committee. In addition, the Pharmacist serving on the IRB is the liaison between the investigators and study staff and the P&T Committee.

The Radiation Safety Officer is the representative for communications with the Radiation Safety Committee. The Radiation Safety Officer is a member of the Radiation Safety Committee, a voting member of the SRS, and EOC Committee.

The ACOS/R&D is a member of the Medical Executive Committee (MEC), which includes the medical center Director and the COS. During this meeting, the ACOS/R&D provides updates on the overall research activities including the HRPP.

The IRB Co-Chairs/R&D Chairperson and Vice-Chairperson(s) have direct access to the COS and medical center Director. PIs have direct access to the COS. Meetings related to the HRPP occur as needed on the request of the COS, the PI, or IRB Co-Chairs/R&D Chairperson, and Vice-Chairperson(s).

EOC Committee communication and information exchange is provided by the RSC and

the Radiation Safety Officer who serve as members of the EOC.

The Research Service provides Research Forums that allow for an exchange of information among Research Service Leadership, investigators, and study staff.

The medical center and Research Service offer an annual “Research Week” where veterans and subjects enrolled in VANEOHS research projects are provided with an opportunity to interact and communicate with researchers.

PCAS and Risk Management are consulted on an as needed basis.

**Interaction among HRPP committees:**

The R&D Committee meeting provides a venue for interaction and communication with other components of the HRPP. Members involved are: ACOS/R&D, AO/R&D, IRB Co-Chairperson, R&D Chairperson, IRB Administrator, a Pharmacy Service Representative, SRS Representative, R&D Committee Coordinator, COS, and the medical center Director.

**Protocol-specific coordination**

The research submission forms, which must be submitted with every protocol, requires PIs to indicate institutional support required for the research.

A letter of support is required from the Out-Patient Clinics Clinical Manager for protocols that involve the use and/or support of the VANEOHS Outpatient Clinics.

## 1.15 HRPP Financial Support

Funding from several sources provide financial support for the HRPP. Funds from VA Central Office provide the revenue required to support the Research Administrative Office which includes the IRB component. The medical center Director supports the salary of the IRB Administrator and the RCO.

VA ORD-allocated funds also support the non-personnel and infrastructural needs of the HRPP program which include: office space and IT equipment, paper, postal and shipping expenses, and education and training. The medical center also provides space for conferences and meetings and audio-visual equipment.

The AO/R&D ensures that the HRPP funding allocation is conducted on a timely and appropriate basis.

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## 1.16 HRPP Resources

The R&D Service, including the HRPP, is located in offices at the VANEOHS Louis Stokes Cleveland VA Medical Center, Research (K) Wing and is equipped with all necessary office space, storage space, and equipment to perform the functions required for the HRPP. The adequacy of personnel and non-personnel resources of the HRPP program is assessed on an annual basis by the ACOS/R&D with the HRPP staff and are

reviewed and approved by the R&D Committee.

## Chapter 2 Institutional Review Board

## 2.1 Purpose

The following describes the authority, role, and procedures of the IRB of the VANEOHS. The IRB is established to ensure the protection of human subjects in research under the auspices of the VANEOHS (See medical center policy 151-002 “Protection of Human Subjects in Research Establishing an Institutional Review Board”). Although the VANEOHS has authorized two IRBs to fulfill this function, both IRBs follow the same policies and procedures. Therefore, for the purposes of this document, all IRBs of the VANEOHS will be referred to as the IRB.

## 2.2 IRB Authority

The R&D Committee and IRB have regulatory authority to take any action necessary to protect the rights and welfare of human subjects in the research program of the VANEOHS. Pursuant to VA regulations at 38 CFR 16.109(a) and under medical center policy 151-018 “Human Research Protection Program,” the IRB is authorized to:

1. Approve, require modifications to secure approval, or disapprove human subject research.
2. Suspend or terminate research for continued noncompliance with the Common Rule, VA, DHHS, and FDA regulations, or its own findings, determinations, and requirements (38 CFR 16.113).
3. Suspend or terminate research that has been associated with unexpected serious harm to participants.
4. Observe and/or monitor VANEOHS research (including the consent process) to whatever extent it considers necessary to protect human subjects.

***All proposed research involving human subjects must be reviewed and approved by both the R&D Committee and the IRB prior to initiation of the research project.***

The IRB functions independently of, but in coordination with, other institutional regulatory committees. The IRB, however, makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected.

## 2.3 Number of IRBs

There is currently one on-site, medical center-wide IRB serving the VANEOHS and the Foundation. The VA does not serve as an IRB of record for any other VA or non-VA facility and/or institution. The VANEOHS also uses the VA Central IRB. See HSP-019 “Use of the VA Central IRB” for a detailed description of the procedures for the use of the VA Central IRB.

## 2.4 Responsibilities

### 2.4.1 IRB

Responsibilities of the IRB are as follows:

1. Review all proposals for research studies involving human subjects, including the full protocol, the informed consent (or a request for waiver if applicable), any Merit Review or grant applications and other supplemental information such as Investigators' Brochures, surveys, questionnaires, advertisements, or other materials provided to the subjects.
2. Approve, disapprove, or make recommendations deemed necessary to qualify the protocol as an acceptable study involving human subjects based upon the minimization of risks to human subjects, a reasonable risk/benefit ratio (i.e., risks to human subjects are reasonable in relation to any anticipated benefits to subjects, and the importance of the knowledge that may reasonably be expected to result from the proposed research), and an assessment of the equitable selection of subjects for the proposed research.
3. Review and approve the informed consent form and ensure that the informed consent form contains all the required elements and meet all other requirements, in accordance with 38 CFR 16.116 and VHA 1200.05 Handbook.
4. The IRB Co-Chairperson or designee review and approve requests for waivers or alterations of authorization for the use and disclosure of protected health information for human subjects research in accordance with the HIPAA Privacy Rule.
5. Ensure additional safeguards have been included in each study to protect the welfare of vulnerable subjects. (The IRB shall consider the inclusion, as regular members or consultants, of one or more individuals who are knowledgeable about and experienced in working with these vulnerable subjects.) See Section 6 "Vulnerable Subjects in Research" for more information.
6. For protocols requiring continuing preview per the common rule continuous review of progress on approved protocols involving human subjects with respect to the degree of risk, its justification and the steps taken to minimize it in view of the cumulative experience with the study or protocol. Continuing review shall occur no less than one year from the date of initial approval or at the interval determined by the IRB. Studies approved under expedited review following the 2018 common rule do not require a continuing review. However, the IRB has the option to require continuing review for 2018 Common Rule expedited studies if they feel it is warranted. Justification for requiring the continuing review must be provided and noted in the IRB minutes.
7. Ensure that steps to manage, reduce, or eliminate potential or real conflicts of interest such as financial/non-financial, role (investigator/patient relationships) and/or institutional have been taken after COI has been reviewed by COI Administrator and all appropriate parties.

8. Determine that the investigator(s) of the proposed research activity have met all current educational requirements for the protection of human subjects as mandated by the VANEOHS FWA, ORD, funding institutions, and OHRP. The IRB must also determine that the investigator(s) are qualified through education, training, and experience to conduct the proposed research.

9. Monitor adequacy of data and safety procedures by reviewing adverse event reports, safety reports from the sponsor, Data Safety Monitoring Board (DSMB) summary reports, and study monitoring or audit reports, if available.

10. Along with the Privacy Officer ensure that adequate provisions are taken by the investigator to protect the privacy of subjects and to maintain the confidentiality of individually identifiable data. Such provisions must consider the requirements of Standards for Privacy of Individually-Identifiable Health Information (HIPAA Privacy Rule), 45 CFR Parts 160 and 164, and other laws regarding the protection and use of veterans' information, including the Privacy Act of 1974, 5 USC 552a; VA Claims Confidentiality Statute, 38 USC 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV) and Sickle Cell Anemia Medical Records, 38 USC 7332; and Confidentiality of Healthcare Quality Assurance Review Records, 38 USC 5705, and VHA Handbook 1605.1 Privacy and Release of Information.

11. Notify the PI and the R&D Committee in writing of its decision to approve or disapprove a proposed research activity, or of modifications required to secure IRB approval.

12. Review and approve all amendments to the protocol or changes to the informed consent prior to the change being initiated, except when necessary to eliminate immediate hazard(s) to the subject(s). If the amendment addresses an issue related to biosafety or radiation safety, the appropriate committee must first approve the amendment.

13. Prepare and maintain adequate documentation of the IRBs activities/actions.

14. Review protocol and consent audits and all findings that are submitted by the RCO to ensure compliance of ongoing human subjects research activities with regulations and policy.

15. Review manuscripts in preparation in which a question is raised about deviations from the approved human studies protocol upon the request of the ACOS/R&D and make recommendations to the R&D Committee of actions to be taken if a deviation from the protocol is verified.

16. Make recommendations to the R&D Committee, ACOS/R&D, COS, and/or medical center Director regarding policy concerning the investigation of new uses of drugs on human subjects or patients.

17. Act in accordance with written procedures, including procedures for:

- Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee;
- Determining which projects require review more often than annually and which

projects need verification from sources, other than the investigator, that no material changes have occurred since the previous IRB review.

- o Ensuring that investigators promptly report proposed changes in a research activity, including amendments to the protocol or the consent form, to the IRB, and ensuring that such changes in approved research are not initiated without the review and approval of the IRB, except when necessary to eliminate apparent immediate hazards to subjects.
- o Reporting promptly to the IRB regarding noncompliance by study staff.
- o Notifying medical center officials, ORO, OHRP, FDA, or VACO of any unanticipated problems that cause harm or risk of harm to human subjects or others; any instance of serious or continuing noncompliance; and suspension or termination of IRB approval in accordance with established SOP Reporting to Regulatory Agencies and Institutional Officials.
- o Reporting any adverse events as required by VA and Federal policy and regulations.
- o Terminating or suspending of IRB approval.
- o Observing the informed consent process.
- o Conducting audits of protocols as needed and other IRB activities.
- o Ensuring that initial education requirements for the IRB Co-Chairperson, IRB members, and IRB alternate members are met.
- o Reporting to the Privacy Officer any unauthorized use, loss, or disclosure of individually identifiable patient information.
- o Reporting violations of VA information security requirements to the ISSO.

18. Retain IRB records in accordance with the VHA's Records control Schedule (RCS 10-1) after the completion of the study and in accordance with the HIPAA Privacy Rule, applicable FDA, and DHHS regulations.
19. Directing unannounced and/or scheduled visits to review PI documents for QA/QI or for any other purposes deemed appropriate by the IRB.

### 2.4.2 R&D Committee:

The responsibilities of the R&D Committee include:

- Providing oversight of the IRB.
- Assuring a scientific review of all research projects conducted at the VANEOHS.
- Maintaining high standards for the quality of the research and for reviewing each project prospectively to ensure the scientific merit and the protection of human subjects.
- Assuring review of research projects to ensure the security of VA data, VA private information, and VA sensitive information.
- Reviewing and approving all HRPP Policies and SOPs.
- Reviewing the actions taken by the IRB with regard to conflicts of interest involving study staff after determinations made by COI Administrator.

- Evaluating potential institutional conflicts of interest and determining what actions are required to avoid, or to appropriately manage, apparent institutional conflicts of interest.
- The R&D Committee will review the activity of the IRB on at least an annual basis and make a determination as to the appropriate number of IRBs that are needed for the medical center.
- The R&D Committee has the authority to review research and approve the research, require modifications to obtain approval, or disapprove the research. It also has the authority to suspend or terminate a research protocol; suspend an investigator's or a research staff member's privilege to conduct research pending appropriate investigation and decision by the medical facility Director; and require the implementation of additional safeguards related to the safety of human subjects, the welfare of research animals, the protections of employees or the environment, or the security of VA Data and VA Sensitive Information.
- The R&D Committee may disapprove a study even if approved by all subcommittees. The disapproval may be based on such issues as inadequate qualifications of the investigator(s); insufficient relevance to the VA's mission; the presence of inadequate resources to conduct the study; the poor design of the study; concerns related to the protection of human subjects, the welfare of animals used in the research, safety to personnel, the environment, or others; unresolved conflicts of interest that may be detrimental to the research or the facility; or other serious concerns as defined by the R&D Committee.
- NOTE: While the R&D Committee can disapprove research approved by one of its subcommittees, it is not permitted to approve research that has been disapproved by an appropriate subcommittee.

### 2.4.3 IRB Administrative Office

The IRB Administrative Office consists of a full-time IRB Administrator, and two full-time IRB Analysts/ The IRB Administrator, with the assistance of the Analysts, is responsible for ensuring that all IRB functions are accomplished in a professional fashion that complies with all relevant regulatory requirements. The IRB Administrative Staff provides administrative and clerical support to the IRB Co-Chairperson and the IRB, as well as scheduling and coordination of the activities of the IRB.

**2.4.3.1 IRB Administrator** The IRB Administrator:

- Directs, coordinates, and oversees all IRB functions and operations.
- Facilitates communications between investigators and the IRB.
- Ensures that study staff added on to human subject protocols has completed the research education requirement and all R&D required credentialing has been checked.
- Oversees and ensures that: a) IRB meetings are scheduled, b) meeting agenda is prepared, c) review materials are complete and distributed for review 5-7 days prior to the meeting, d) decisions are communicated to investigators in a

reasonable time, e) minutes are recorded accurately and convey IRB deliberations and contingencies for approval, f) reports are obtained and generated on time, and g) records are maintained.

- Interprets and applies federal, state, and VA regulations, medical center policies, human research protection policies, procedures, and guidelines to protect human subjects and to ensure institutional compliance.
- Prepares presentations for the IRB on ethical and regulatory topics.
- Provides regulatory and ethical, advice to investigators, staff, and students in preparation of application for research protocols involving human subjects.
- Advises and educates investigators and all study staff regarding operational procedures for obtaining and maintaining IRB approval to conduct research.
- Develops and presents educational materials for investigators, staff, and students on the ethical conduct of research involving human subjects.
- Provides orientation and training of IRB members.
- Assists in program development, implementation, and evaluation of the human research protection program.
- Leads the IRB component of regulatory site visits.
- Maintains and reports changes in IRB membership to OHRP and ORO. An updated roster will be submitted to ORO within 30 days of any change in membership.
- Maintains and reports changes in the FWA to OHRP and ORO.
- Interviews, orients, directs and educates the IRB staff.
- Maintains quality control of IRB support functions.
- Serves as a voting member of the Case IAC.

**2.4.3.2 IRB Analyst** The IRB Analyst:

- Assists in facilitating communications between investigators and the IRB.
- Assists in preparing IRB meeting agendas, preparing review materials for the agenda, preparing correspondence conveying IRB deliberations and contingencies for approval.
- Assists in interpreting and applying federal, state, and VA regulations, medical center policies, human research protection policies, procedures, and guidelines to protect human subjects and to ensure institutional compliance.
- Provides regulatory and ethical advice to investigators, staff, and students in preparation of application for research protocols involving human subjects.
- Advises and educates investigators and all study staff regarding operational procedures for obtaining and maintaining IRB approval to conduct research.
- Assists in the orientation and training of IRB members.
- Maintains accurate and complete records using the computerized database system for tracking purposes.
- Maintains the security of IRB records and documents.
- Assists the IRB Co-Chairperson and Administrator in assigning reviewers for all new studies on the IRB agenda.
- Receives, triages, and distributes adverse event reports and reports of

unanticipated problems to the IRB Co-Chairperson, IRB primary reviewer, or for review at the convened IRB meeting.

- Reviews all study submissions coming into the IRB office for completeness, accuracy of content, appropriate forms, documents, attachments, and signatures.
- Verifies that staff listed on human subject protocols have completed the research education requirement and all R&D required credentialing has been checked.
- Provides feedback on ways to improve IRB office functions.
- Communicates with RCC on research credentialing matters.

## 2.5 Roles and Responsibilities

### 2.5.1 IRB Co-Chairperson

The IRB Co-Chairperson's responsibilities are as follows:

1. Plays a leadership role in establishing and implementing IRB policy in conjunction with the IRB Administrator, R&D Committee, ACOS/R&D, COS, and medical center Director.

2. Represents the IRB in discussing IRB decisions with researchers.

3. Represents the IRB in discussions with other segments of the organization.

4. Represents the VANEOHS in discussions with federal and regulatory authorities.

5. Reviews all protocols presented to the full committee and communicates with the IRB Administrator and other reviewers so that important IRB issues are identified and/or resolved before the full committee meeting.

6. Directs the proceedings and discussions of the convened IRB meeting. This includes keeping the discussion focused on important IRB issues and ensuring that the convened committee meeting process is both efficient and effective.

7. Serves as an IRB voting member.

8. Demonstrates an in-depth understanding of ethical issues, federal, state, and VA regulations, medical center policies, human research protection policies, procedures, and guidelines to protect human subjects and to ensure institutional compliance.

9. Consults the IRB Administrator to ensure that the operation of the IRB is within all applicable regulatory requirements.

10. Reviews the IRB minutes that document a summary of the protocol, pertinent IRB discussions, issues, and concerns raised by the IRB, and actions and reasons for the actions taken by the IRB.

11. Reviews and acts on requests for IRB exemption assuring that studies that receive exemption have met the requirements. Those studies that do not qualify for exempt review will be sent to the IRB for review.

12. May delegate expedited review request to experienced IRB member, who

will then act on the request on behalf of the IRB. Those studies that do not qualify for expedited review will be sent to the convened IRB for review.

13. Reviews or delegates the review, of responses from investigators to determine if they responded sufficiently to the IRB's concern to allow approval under expedited review procedures and without being returned to the fully convened IRB.

14. Assists in the review of serious Unanticipated Problems and determines if appropriate action, if any was taken by the PI and if any additional action is necessary regarding patient safety. The IRB Co-Chairperson will also determine if any changes to the protocol or consent form are necessary from that point forward. In the cases of Unanticipated Problems that have seriously compromised patient safety, the IRB Co-Chairperson will ask the PI to offer an explanation and will report such incidents to the R&D Committee, the COS, and the medical center Director.

15. Reports to appropriate regulatory agencies and organizations, when necessary, consistent with VA policy and federal regulations.

### 2.5.2 IRB Members

The IRB members' responsibilities are as follows:

1. Assuring that the rights and welfare of research subjects are protected.

2. Participating in training and continuing education on ethical, legal, and regulatory issues related to the IRB. All members are required to complete the research education requirements.

3. Reviewing assigned protocols and completing a Checklist with special attention to the consent form content, scientific, ethical, administrative, and other pertinent issues related to specific research.

4. Prior to the convened meeting, contacting individual investigators directly, for clarification as needed so that important IRB issues are identified and/or resolved before the full committee meeting

5. Maintaining appropriate confidentiality of the information contained in any and all reviews.

6. Listening and taking part in active IRB discussions and contributing in his/her area of expertise as appropriate. When appropriate, asking questions for clarification to aid in the decision-making process.

7. Making an informed vote to approve, grant contingent approval, defer for major modifications, or disapprove the research protocol as presented to the IRB.

8. Conducting expedited reviews.

9. Avoiding conflicts of interest or the appearance of conflicts of interest

10. Becoming familiar and knowledgeable of all human subjects research policies and procedures, and the HRPP SOPs.

### 2.5.3 Alternate IRB Members

Alternate members serve in the absence of the primary IRB member for whom they have been designated as an alternate. Typically, the alternate member serves the same term length as the primary member, usually three years. The alternate member has the same level of expertise as the primary member for whom he/she serves as an alternate. The IRB roster identifies the primary member for whom each alternate member may substitute.

Alternates may attend any IRB meeting and are encouraged to attend as many meetings as possible. The alternate member will not be counted as a voting member unless the primary member is absent. However, the alternate member may freely participate in the discussion. IRB minutes will record when alternate members act in the absence of the primary members. All alternate members will receive the same reviewer information as the primary IRB members when they attend meetings for the absent primary member.

### 2.5.4 Ex Officio Members

Ex officio members are appointed due to their position at the VANEOHS and attend IRB meetings as needed to provide input to the IRB deliberations. These members do not vote and are not counted as part of the quorum, but must adhere to the same institutional, regulatory, and federal, and COI policies and procedures and are required to take the same training as voting IRB members.

## 2.6 IRB Membership

IRB members are selected based on appropriate diversity, including consideration of race, gender, cultural backgrounds, specific community concerns in addition to representation by multiple, diverse professions, knowledge and experience with vulnerable subjects, and inclusion of both scientific and non-scientific members. The structure and composition of the IRB must be appropriate to the amount and nature of the research that is reviewed. Every effort is made to have member representation that has an understanding of the areas of specialty that encompasses most of the research performed at the VANEOHS. The VANEOHS has procedures that specifically outline the requirements of protocol review by individuals with appropriate scientific or scholarly expertise.

An understanding of and specific sensitivity to the veteran population is also a consideration of membership. In addition, the IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in VANEOHS research.

## 2.7 Composition of the IRB

1. The IRB will have at least five members with varied backgrounds to promote complete and adequate review of research activities commonly conducted at the VANEOHS.
2. The IRB members will be sufficiently qualified to review the research through their experience, expertise, and diversity, including race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes. The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities.
3. The IRB will be able to ascertain the acceptability of proposed research in terms of institutional policies and regulations, applicable law, and standards of professional conduct and practice. The IRB will therefore include persons knowledgeable in these areas.
4. The IRB will have at least one member (non-affiliated) who is not affiliated with the VANEOHS and who is not part of the immediate family of a person who is affiliated with the VANEOHS. He/she may include a member of the clergy, an attorney, or a representative of a legally recognized veterans organization that can provide consideration of ethical and legal issues involved in participation of human subjects in research.
5. The IRB will have at least one member whose area of expertise is non-scientific in nature. This person **must** always be present to have a quorum.
6. The IRB will have at least one member with expertise in scientific areas. Emphasis shall be made on special fields of expertise in the specific types of research activities conducted at the VANEOHS.
7. The IRB will have at least one members who is interested and/or who has experience with vulnerable populations typically involved in research at the VANEOHS.
8. The IRB will have Co-Chairperson(S) with a VA compensated appointment.

## 2.8 Appointment of Members to the IRB

The nomination for IRB Co-Chairperson is submitted by the IRB to the medical center Director who formally appoints him/her in writing. The IRB Co-Chairperson must hold a VA appointment, in a compensated capacity. He/she should be a highly respected individual fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The IRB Co-Chairperson serves a three-year term and may be re-appointed indefinitely without lapses in service.

Nominations for IRB Members are submitted by the IRB to the medical center Director who formally appoints them in writing. IRB members must hold a VA appointment in

either a compensated or non-compensated capacity. Members serve three year terms and may be reappointed without lapses in service.

## 2.9 IRB Member Conflict of Interest

No regular or alternate member may participate in the review (initial, continuing, modification, non-compliance, or unanticipated problem) of any research project in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB member and ex-officio member to disclose any COI in a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room. Members who are assigned to review research in which they have a conflict of interest must notify the IRB Administrator, IRB Coordinator or IRB Program Assistant.

In addition, the IRB Co-Chairperson or IRB Administrator will poll IRB members at each convened meeting to determine if a COI exists regarding any protocols to be considered during the meeting. The Member(s) are reminded that they should recuse themselves by leaving the room during the discussion and vote of the specific protocol. IRB members with a conflicting interest are excluded from being counted towards quorum. All recusals by members with COI are recorded in the minutes.

Committee members may find themselves in any of the following conflicts of interest when reviewing research:

1. Where the member or consultant is involved in the design, conduct, and reporting of the research.
2. Where the member or consultant competes for research grants or contracts in the same or similar field as an investigator whose research is scheduled for review.
3. Where an immediate family member of the member or consultant is involved in the design, conduct, and reporting of the research.
4. Where the member or an immediate family member holds significant financial interests in the research being reviewed.

## 2.10 Use of Consultants

An occasion may arise in which a study or an issue raised within or related to a study is presented to the IRB where no member possesses the specialty, knowledge, and/or expertise to adequately review the protocol. The IRB and/or The IRB Administrator or Staff may, at its discretion, engage the services of individual(s) who possess a particular expertise. The individual will review the protocol and will either discuss the protocol before the convened IRB or provide a written document that addresses specific questions proposed by the IRB. The need for a consultant should be identified as early in the research review process as possible. The convened IRB may require that a consultant review a specific protocol. If the IRB determines that a consultant review is

required, the protocol will be deferred to a future meeting.

The IRB Co-Chairperson or the convened IRB will make the final determination whether a consultant is needed. Recommendations for consultants may come from the ACOS/R&D, IRB Co-Chairperson, IRB members, R&D committee members, COS, and/or Clinical Service Chiefs. Consultants can be staff members of the VANEOHS, staff members of the affiliated University and medical centers, or other individuals who possess expertise in the discipline/field that is the focus of the research protocol. The IRB Co-Chairperson will identify the specific issues for the consultant's consideration.

Consultants may not be part of the study team nor may they have any potential financial, or non-financial, conflicts of interest with the proposed research under review. **Consultants must comply with the same requirement for conflict of interest of IRB members and financial conflict of interest policies**

The IRB Administrator will act as the primary liaison between the IRB and the consultant. The IRB Administrator will contact the consultant and request his/her review of the given research protocol. The IRB Administrator will review the conflict of interest form and the financial conflict of interest policy for IRB members with the consultant who will verbally confirm to the IRB Administrator they do not have a conflict of interest prior to review.

If no conflicts are identified, the IRB Administrator will document this in the study file, will send the consultant a statement of confidentiality, a request for a current CV, the protocol and all applicable documents along with a letter outlining areas of consideration.

When the consultant is present at the convened IRB meeting, the consultant may participate in IRB deliberations, and make recommendations to influence IRB determinations. However, consultants may not vote and will not be included in the establishment of a quorum at the respective IRB meeting.

The IRB uses the CV or qualifications of the consultant in order to evaluate the weight to be given to his/her recommendations during protocol review. The minutes will reflect the use of the consultant and the reasons for seeking outside guidance. Key information provided by consultants at meetings will be documented in the minutes.

The IRB may request further information from the consultant, if so this will be documented in the IRB minutes and sent to the consultant by the IRB Administrator

Ad hoc or informal consultations requested by individual members (rather than the full board) will be requested in a manner that protects the researcher's confidentiality and is in compliance with the IRB conflict of interest policy (unless the question raised is generic enough to protect the identity of the particular PI and research protocol).

## 2.11 Training / Ongoing Education of IRB Co-Chairperson, IRB Members, and Staff

A vital component of a comprehensive human research protection program is an education program for the IRB Co-Chairperson, the IRB members, and the IRB Administrative Staff. The VANEOHS is committed to providing training and an on-going

educational process related to ethical concerns and regulatory and institutional requirements for the protection of human subjects.

All IRB members and IRB Administrative Staff are required to complete the research education requirement and the credentialing. See Section 11 “Education and Credentialing for Employees Involved in Human Subjects Research.”

**Orientation of New IRB Voting Members**

Once the IRB voting member has been appointed by the medical center Director and has completed the research education and credentialing process, The IRB Administrator will initiate the orientation process. The following subjects and materials may be reviewed:

- Belmont Report
- “Institutional Review Board Member Handbook” (2011) by Robert Amdur, M.D.
- Website link to IRB Forms and information
- Reviewer Checklists

Once an IRB voting member has been added to the official IRB Roster, the IRB member will be required to vote if designated as a permanent IRB member, or will be eligible to vote if designated as an alternate member (in the absence of the permanent IRB member). If an IRB voting member, once added to the official roster, is not comfortable voting on a given study, he/she may abstain from voting. This will be documented in the IRB minutes.

IRB voting members will be assigned as a primary or secondary reviewer when/as they demonstrate readiness and a desire to be

New IRB members assigned as a primary or secondary reviewer for their first study reviewed by the convened Board will be paired with an experienced IRB member.

IRB members, as determined to be qualified by the IRB Co-Chairperson or IRB Administrator, will be assigned to review studies utilizing an expedited review process. The IRB Co-Chairperson or IRB Administrator uses the following criteria to select an IRB member to serve as Co-Chairperson Designee when conducting expedited review:

- Voting member of the IRB
- Expertise in the area of research to be reviewed

The IRB Co-Chairperson will oversee several of the studies that the new member reviews under expedited review to ensure compliance with the applicable regulations. The IRB Co-Chairperson will provide feedback to the IRB member as to the quality of the review.

**Orientation of Ex officio Members and IRB Staff**

Once the Ex officio members and IRB staff have completed the research education and credentialing process, The IRB Administrator will initiate the orientation process. The following subjects and materials may be reviewed:

- Belmont Report
- Institutional Review Board Member Handbook (2011) by Robert Amdur, M.D.
- IRB Member Conflict of Interest Assessment Form
- Website to IRB Forms and information
- HRPP SOP

**Continuing Education**

To ensure that oversight of human research is ethically grounded and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members and staff throughout their service on the IRB. Multiple avenues of educational opportunities are available locally and nationally. Educational activities include, but are not limited to;

1. In-service and educational offerings at convened IRB meetings.
2. Case IRB Member Symposium.
3. Research Service Research Forums.
4. Identification and dissemination by the ACOS/R&D, IRB Co-Chairperson, RCO, or IRB Administrator of new information that might affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues to IRB members and staff via email, mail, or during IRB meetings.
5. Opportunities to attend national and local human subject protection related conferences and seminars (PRIM&R, ORPP&E educational offerings, OHRP educational offerings, etc.).
6. Access to a variety of human subject research references located in the IRB Office such as:
    - Amdur, R. (2011). Institutional review board member handbook. Sudbury, MA: Jones and Bartlett Publishers.
    - Dunn, C.M. & Chadwick, G.L. (2002). Protecting study volunteers in research: a manual for investigative sites. Boston, MA: Thomson CenterWatch.
    - Bankert, E. A., Gordon, B.G., Hurley, E.A., and Shriver, S.P. (2022). Institutional Review Board Management and Function. Burlington, MA: Jones and Bartlett Learning.

## 2.12 Compensation of IRB Members

The VANEOHS does not provide monetary compensation to VA employees for their

service on the IRB. However, it is acknowledged that service on the IRB requires a significant investment of time for all IRB members and especially for IRB Co-Chairpersons.

## 2.13 Liability Coverage for IRB Members

Actions for alleged negligence or wrongful acts or omissions of Federal employees come within the provisions of the Federal Tort Claims Act (FTCA). The coverage extends to the federally employed IRB members acting in performance of their duties.

To extend coverage to non-federally employed IRB members acting in performance of their IRB duties, the non-federally employed IRB members (e.g., non-affiliated or community members) shall have VA WOC appointments. VACO has concluded that WOC status does not diminish their “independent/non-affiliated” capacity as required by the human subject protection regulations.

## 2.14 Collaborative Research Projects

In the conduct of collaborative research projects, the VANEOHS acknowledges that each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations.

**IRB of Record Approval**

Each collaborating institution engaged in human subjects research must obtain approval from its IRB of Record and hold an FWA or another assurance acceptable to VA (e.g. DoD assurance).

VA investigators must submit a protocol or other documentation to the VANEOHS IRB that clearly delineates which research activities will be conducted as the VA portion of the overall Collaborative Research study (e.g., by VA investigators on VA time or VA property).

Each institution engaged in the Collaborative Research must use the informed consent document and HIPAA authorization required by its respective institutional policies for subjects recruited from that institution, or procedures requiring participation of the subjects at that institution. The informed consent document may contain information on the project as a whole as long as the document clearly describes which procedures will be performed under VA’s auspices and which will be performed under a non-VA institution’s auspices.

The VA informed consent document must clearly state when procedures conducted at other non-VA institutions are part of the VA’s portion of the study.

The informed consent document and HIPAA authorization (for the VA portion of the collaborative study) must not contain inconsistent provisions.

**Research Data**

The protocol, addendum, and/or IRB of Record application must describe the data to be disclosed to collaborators, the entities to which the data are to be disclosed, how the data are to be transmitted, and how the transmitted data will be stored, retained,

destroyed, and/or further disclosed and to whom. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data.

All disclosures and data transmission must meet VA privacy and security requirements per VA Directive 6500, Managing Information Security Risk: VA Information Security Program, dated September 20, 2012; VA Handbook 6500, Risk Management Framework for VA Information Systems – Tier 3: VA Information Security Program, dated March 10, 2015; and VHA Directive 1605.01, any superseding policies.

Agreements regarding data use and transmission must be executed as required as applicable in VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research, dated March 9, 2009, or any superseding policies revising or replacing it. NOTE: This directive does not preclude other applicable agreements required for the Collaborative Research (e.g., data use agreement).

## 2.14 International Research

All human subject research in which investigators from VANEOHS are involved must comply with all applicable federal regulations for the protection of human subjects in all material respects. This includes research conducted by investigators in foreign countries.

VA international research is defined as any VA-approved research conducted at international sites (i.e., not within the United States (U.S.), its territories, or Commonwealths), any VA-approved research using either identifiable or de-identified human biological specimens or identifiable or de-identified human data originating from international sites, or any VA-approved research that entails sending such specimens or data out of the U.S. This definition applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including MOUs, CRADAs, grants, contracts, or other agreements. ***NOTE:*** *For the purposes of this SOP, research conducted at U.S. military bases, ships, or embassies is not considered international research.*

- Sending specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site) is considered international research. Remote use of data that is maintained on VA computers within the U.S. or Puerto Rico and U.S. territories accessed via a secure connection is not considered international research.

- International research includes multi-site trials involving non-U.S. sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the Investigational New Drug (IND), or the VA manages the data collection and the data analyses.

- International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).

Before approving international research involving human subjects research, the IRB must ensure that human subjects outside of the U.S. who participate in research projects in which VA is a collaborator receive equivalent protections as research participants inside the U.S. if the activity involves human subjects research requiring IRB approval or limited IRB review (see OHRP guidance at: http://www.hhs.gov/ohrp/international/index.html ). The facility Director must approve participation in the proposed international research (see guidance at: http://www.research.va.gov/resources/policies/default.cfm ).

All international research must also be approved explicitly in a document signed by the VA medical facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO.

## 2.15 Reporting and Investigation of Allegations of Undue Influence

If an IRB Co-Chairperson, member, or staff person considers that the IRB has been unduly influenced by any party, he/she shall make a confidential report to the IRB Co-Chairperson, R&D Committee and/or ACOS/R&D, depending on the circumstances. The ACOS/R&D will conduct a thorough investigation and report his/her findings to the medical center Director through the COS. Final corrective action recommended by the medical center Director will be taken to prevent additional occurrences.

## Chapter 3 IRB Review Process

### 3.1 Purpose

All human subjects research conducted under the auspices of the VANEOHS must meet the criteria for one of the following methods for review:

- Exempt
- Expedited Review
- Full Committee Review

The IRB will ensure that the research meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research.

The following describe the procedures required for the review of research by the IRB

### 3.2 Definitions

**Minimal Risk.** Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**Minor Change**. A minor change is one that, in the judgment of the IRB reviewer, makes no substantial alteration in:

1. the level of risks to subjects.
2. the research design or methodology (adding procedures that are not eligible for expedited review would not be considered a minor change).
3. the number of subjects enrolled in the research.
4. the qualifications of the study staff.
5. the facilities available to support safe conduct of the research.
6. the likelihood of subjects willingness to participate.
7. any other factor which would warrant review of the proposed changes by the convened IRB.

**Quorum.** A quorum of the IRB consists of a simple majority of the voting membership, including at least one member whose primary concern is in a non-scientific area. If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum.

**Suspension of IRB approval.** A suspension of IRB approval is a directive of the convened IRB or other authorized individual to temporarily stop some or all previously approved research activities. Suspended protocols remain open and require continuing

review.

**Termination of IRB approval**. A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

## 3.3 Human Subject Research Review Process

### 3.3.1 Human Subjects Research Consultation

Investigators and study staff are encouraged to meet with the applicable Research Service Staff to discuss the submission of new human subjects protocols. Meetings allow for study-specific consultation and guidance when preparing the protocol application materials. IRB specific topics addressed in this meeting include but are not limited to: a) specific questions about the HRPP policies and procedures, b) determination of whether a particular protocol is human subject research or not, and c) what forms are required for a particular study. R&D specific topics addressed in a meeting include but are not limited to: a) questions about required R&D forms, b) guidance on types of reviews and reviewers required by R&D, c) data security and data base questions, d) budget guidance.

## 3.4 Human Subjects Research Determination

The responsibility for initial determination as to whether an activity constitutes human subjects research rests with the investigator. The investigator should make this determination based on the definitions of “human subject” and “research” Since the VA will hold the investigator responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subjects research from the appropriate source. These sources include but are not limited to VHA Program Manager, Institutional Official or designee, ACOS/R&D or IRB Co-Chairperson. The request may be made verbally, by phone contact, by email, or through a formal written communication. All requests must include sufficient documentation of the activity to support the determination.

### 3.4.1 Definitions

For the purposes of this policy, a **“systematic investigation”** is an activity that involves a prospective study plan which incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

Research as defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of

the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act" means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]
- Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act" means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]"

**Human Subject**. A human subject is a living individual about whom an investigator (whether professional or student) conducts research, and: (1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (2) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

- Intervention as defined by VA regulations means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- Interaction as defined by VA regulations means communication or interpersonal contact between investigator and subject.
- Private information as defined by VA regulations means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.
- Identifiable private information as defined by VA means information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

## 3.5 Quality Assurance/Quality Improvement Activities.

Quality assurance activities attempt to measure the effectiveness of programs or services. Quality assurance activities that are designed solely for the purpose of internal

program evaluation, with no external application or generalization, are not considered human subjects research and do not require IRB review. If the activities meet the definition for human subjects research then R&D Committee and IRB review are required.

## 3.6 Research Activities vs. Innovative Treatments in Medical Practice.

In the course of medical practice, sound clinical judgment sometimes leads physicians to employ “innovative” treatments where more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient’s individual needs. Such innovative treatments, employed on an occasional basis and solely for clinical purposes, do not normally constitute human subject research and do not normally require IRB review. However, the use of innovative treatments as part of a systematic investigation designed, at least in part, to develop or contribute to generalizable knowledge does constitute human subject research and does require prospective R&D Committee and IRB review.

## 3.7 Research Activities vs. Medical Case Reports.

Generally speaking, a case report is not considered research because it is not “a systematic investigation designed to develop or contribute to generalizable knowledge;” therefore, it does not come under the rubric of the IRB or R&D Committee. Further, the case report presentation, whether by lecture or publishing, is executed by the physician of record, meaning that the patient's own physician is reporting the case and already has identified the patient and has access to the clinical data. If the presentation uses photographs, initials, or any other information that may possibly identify the patient, then a medical center consent form for this purpose is required.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review research and then requires IRB and R&D Committee review. Usually, a case report summarizes a small number of cases to emphasize a discrete instance of disease. However, it is the nature of the report, not the absolute number of cases, that determines whether or not the activity involves human subjects research. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subjected to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at a least a systematic qualitative analysis that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

## 3.8 Research Activities vs. Commercial Services.

VANEOHS facilities and laboratories may occasionally provide tests or other services to non-VANEOHS researchers solely on a commercial basis.

Provision of such services solely on a commercial basis does not constitute human subject research and does not require VANEOHS IRB review, provided that all of the following conditions are met:

- The research is not otherwise conducted at VANEOHS;
- The research does not otherwise involve VANEOHS employees or agents (e.g., as co-investigators, in planning or analysis, or receiving publication credit);
- The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges;
- The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality; and
- The commercial services are conducted under a valid contract.

However, if VANEOHS personnel are involved in any way that is more than merely providing a commercial service, then prospective review and approval by the R&D Committee and IRB is required.

## 3.9 Exempt Studies

Under certain circumstances, human subjects research may be exempt from IRB review. Investigators may not make an independent determination that research is exempt from IRB review.

### R&D Committee Responsibility

For exempt studies, the R&D Committee will be the Committee of record for the study and will notify the PI when final approval has been granted. f an exempt activity requires a limited IRB review, the limited IRB review must be completed prior to approval by the R&D Committee

### 3.9.1 Categories of Exempt Research

With the exceptions listed below, research activities not regulated by the FDA in which the only involvement of human subjects will be in one or more of the following categories are exempt from IRB review, but require institutional and/or R&D Committee review, at VANEOHS:

### 3.9.2 CATEGORIES OF EXEMPT RESEARCH:

### USE OF CATEGORIES

Use of the exemption categories for research subjects who are pregnant women, prisoners, or children is as follows:

a. **Pregnant Women.** Each of the exemptions section may be applied to research involving pregnant women if the conditions of the exemption are met.

b. **Prisoners.** The exemptions at this section do not apply to research involving prisoners, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

c. **Children.** The exemptions for Categories 1, 4, 5, 6, 7, and 8 may be applied to research subjects who are children if the conditions of the exemption are met. Exempt category 2(a) and (b) of this section may only apply to research subject to 45 CFR 46 subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Category 2 (3) of this section may not be applied to research subject to subpart D

**Category 1.** Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

**Category 2.** Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) **if at least one of the following criteria is met:**

(1) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(2) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(3) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination.

***NOTE:*** *The exemption for research involving survey or interview procedures or observations of public behavior does not apply to research involving children, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.*

**Category 3.** Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection **and at least one of the following criteria is met:**

(1) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(2) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(3) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review.

(4) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(5) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

**Category 4.** Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, **if at least one of the following criteria is met:**

(1) The identifiable private information or identifiable biospecimens are publicly available;

(2) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(3) The research involves only information collection and analysis involving the investigator’s use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of health care operations or research as those terms are defined at 45 CFR 164.501 or for public health activities and purposes as described under 45 CFR 164.512(b); or

(4) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities; if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with

section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note; if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a; and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

**Category 5.** Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs.

(1) Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(2) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

***NOTE:*** *The determination of exempt status for research and demonstration projects meeting the criteria in paragraph Category 5 must be made by the Under Secretary for Health on behalf of the Secretary of VA, after consultation with Office of Research and Development (ORD), Office of Research Oversight (ORO), Office of General Counsel (OGC), and other experts, as appropriate.*

**Category 6.** Taste and food quality evaluation and consumer acceptance studies:

(1) If wholesome foods without additives are consumed, or

(2) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

<u>As of the approval of this SOP, the VA northeast Ohio Healthcare System will not be using Categories 7 and 8 which involve the use of Broad Consent.</u>

### 3.9.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR 56.104(c)]

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

### 3.9.4 Additional Protections

Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report. The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

## 3.10 Expedited Studies

The IRB Co-Chairperson, or designee, or IRB Administrator will make a determination on whether or not a protocol may be reviewed using expedited procedures. The individual(s) making this determination cannot be involved in the proposed research. The determination on whether or not a protocol may be reviewed using expedited procedures is based on either one or both of the following:

1. The research is not greater than minimal risk and falls into one of the categories appearing on the list found at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/categories-of-research-expedited-review-procedure-1998/index.html .
2. The research constitutes a minor change in previously approved research during the period of one year or less for which approval is authorized, where study was initially approved by full board.
3. 2018 Common Rule -Research for which limited IRB review is a condition of exemption.

The Co-Chairperson, or IRB Administrator may designate a qualified designee to complete the review of the request and research project. The qualified designee must

have, experience and knowledge in the content of the protocol to be reviewed, as well as be knowledgeable of the requirements to approve research under expedited review. The reviewer may exercise the authority of the IRB, but may not disapprove the research. If the IRB Co-Chairperson or qualified designee does not approve the research through expedited procedures, then the research project will be reviewed by the convened IRB which may disapprove the research.

When reviewing research under an expedited review procedure, the reviewer receives and reviews all documents, including the complete protocol that would normally be submitted for a full-board review. The reviewer(s) conducting initial or continuing review complete the appropriate “Reviewer Checklist” to determine whether the research meets the criteria allowing review using the expedited procedure and if so, whether the research meets the regulatory criteria for approval. The results of the review, including a determination of the regulatory criteria for use of such a review procedure, are documented by a signed “Reviewer Checklist.”

The full IRB will be notified of all research approved under expedited procedures through the IRB meeting agenda and minutes. All correspondence resulting from an expedited review will note the results of the review. Documentation for expedited reviews maintained in IRB records shall include the category and circumstances that justify using expedited procedures.

Please note that any individual involved in conducting an expedited review of a proposed research project cannot be involved in the proposed research.

### 3.10.1 Categories of Research Eligible for Expedited Review

The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

- The categories in this list apply regardless of the age of subjects, except as noted.
- The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
- The expedited review procedure may not be used for classified (withheld from general circulation for reasons of national security) research involving human subjects.
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

**Research Categories one (1) through seven (7) pertain to both initial and continuing IRB review:**

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
    a. Research on drugs for which an investigational new drug application (IND) (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
    b. Research on medical devices for which (i) an investigational device exemption (IDE) application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
    a. from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
    b. from other adults and children[1], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week. [[1]Children are defined in the DHHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."][45 CFR 46.402(a)]

3. Prospective collection of biological specimens for research purposes by noninvasive means. For example:
    a. hair and nail clippings in a nondisfiguring manner;
    b. deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
    c. permanent teeth if routine patient care indicates a need for extraction;
    d. excreta and external secretions (including sweat);
    e. uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue;
    f. placenta removed at delivery;
    g. amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;
    h. supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;
    i. mucosal and skin cells collected by buccal scraping or swab, skin swab, or

mouth washings;
j. sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) For example:
    a. physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
    b. weighing or testing sensory acuity;
    c. magnetic resonance imaging;
    d. electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
    e. moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(4). This listing refers only to research that is not exempt.]

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. [NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.]

8. Continuing review of research previously approved by the convened IRB where:
    **a.** the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; **or**
    **b.** no subjects have been enrolled and no additional risks have been identified; **or**

c. the remaining research activities are limited to data analysis.

[Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.]
For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8) a., b., or c. are satisfied for that site. However, with respect to category 8 b., while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.]

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

[Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories 2 through 8 do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified. The determination that "no additional risks have been identified" does not need to be made by the convened IRB.]

NOTE: For studies approved under expedited review that were approved under or transitioned to the 2018 Common rule a continuing review is not required, unless otherwise determined by the IRB.

## 3.11 Convened IRB Meetings

Except when an expedited review procedure is used or when a limited IRB review process is used, the IRB will conduct initial and continuing reviews of all research at convened meetings at which a quorum of the members is present.

### 3.11.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year. The schedule for the IRB may vary due to holidays or lack of quorum. The IRB Co-Chairperson may determine that special and/or additional meetings are necessary. The schedule for IRB meetings can be found on the Research Service website**.** Additionally, this information is available in the IRB Office and is posted for the benefit of all investigators, research coordinators, and other study staff when submitting protocol materials.

### 3.11.2 Quorum

A quorum consists of a simple majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. The Community Member, who represents the general perspective of subjects, is required to be present for at least 10 of 12 meetings.

If research involving an FDA-regulated article is involved, a licensed physician must be included in the quorum. The IRB Co-Chairperson, with the assistance of the IRB Administrative Staff, will confirm that an appropriate quorum is present before calling the meeting to order. The IRB Co-Chairperson and IRB Administrator and/or Staff will be responsible for ensuring that the meetings remain appropriately convened.

A quorum must be maintained for each vote to occur. The IRB Administrator and/or Staff takes note of arrivals and departures of all members and notifies the Co-Chairperson if a quorum is not present. If a quorum is not maintained, the proposal must be tabled or the meeting must be terminated. All members present at a convened meeting have full voting rights, except, in the case of a conflict of interest (see below), or if an alternate member is present in addition to the primary member. In order for the research to be approved, it must receive the approval of a majority of the voting members present at the meeting.

Members are considered present if they are participating through teleconferencing or videoconferencing. In this case the member must have received all pertinent material prior to the meeting and must be able to participate actively and equally in all discussions.

Opinions of absent members that are transmitted by mail, telephone, facsimile or e-mail may be considered by the attending IRB members but may not be counted as votes or to satisfy the quorum for convened meetings.

### 3.11.3 Pre-Meeting Distribution of Documents

The schedule for submission of materials can be found on the website. Schedule may vary due to holidays. The meeting agenda will be prepared by the IRB Administrative Staff and available in VAIRRS/IRBNet prior to the IRB meeting. Meeting materials are available 5-7 days before the scheduled meeting to allow sufficient time for the review process.

### 3.11.4 Meeting Procedures

The IRB Co-Chairperson will call the meeting to order, once it has been determined that a quorum is in place. The Co-Chairperson or Administrator will poll members to determine if a Conflict of Interest exists. regarding any protocols to be considered during the meeting and remind them that they should recuse themselves by leaving the meeting during the discussion and vote on the specific protocol. The IRB will review and discuss IRB minutes from previous meeting(s) (as applicable). If there are no changes to be made, the minutes will be approved as presented and considered final. If it is determined

that revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting. The IRB Administrator will forward approved IRB minutes to the R&D Committee for review.

The IRB Administrator is responsible for recording the proceedings of the session and preparing final minutes for each IRB meeting.

### 3.11.5 Guests

At the discretion of the IRB, a PI and/or designee may be invited to the IRB meeting to answer questions about their proposed or ongoing research. The PI and/or designee may not be present for the discussion or vote on their research.

Other guests may be permitted to attend the IRB meetings at the discretion of the IRB Co-Chairperson or the IRB Administrator. Guests may not speak unless requested by the IRB. All guests are reminded that all discussions are to be kept in the strictest confidence. Guests may not be present for the discussion or vote of research in which they are involved.

### 3.11.6 Primary Reviewers

The IRB, Administrator and or IRB Staff will assign primary reviewers to new protocols based on the scientific content of the protocol and the reviewer's expertise, discipline, interests, and prior reviewer experience. One or two reviewers will be assigned to each new protocol and when possible will remain the reviewers for the life of the study (i.e. the same reviewers will be used for continuing reviews, modifications, and any other study related matters). When the IRB is presented with a study that may be outside of the knowledge base of any of the IRB members, an outside consultant will be sought.

Primary reviewers will be listed on the IRB agenda.

The primary reviewers are responsible for:

1. Having a thorough knowledge of all of the details of the proposed research.
2. Performing an in-depth review of the proposed research.
3. Leading the discussion of the proposed research at the convened meeting, presenting both positive and negative aspects of the research, and leading the IRB through the regulatory criteria for approval.
4. Communicating with the PI or staff pre-meeting to get clarification on major issues and to make suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms.

If the primary reviewers are absent from the meeting, a new reviewer may be assigned by the IRB Co-Chairperson, Administrator and or the IRB Staff providing the new reviewer has reviewed the materials prior to the meeting. Additionally, an absent

reviewer can submit his/her written comments for presentation at the convened meeting, as long as there is another reviewer present at the convened meeting, who can serve as the primary reviewer. The IRB co-chair will present comments for absent reviewers.

Note: All IRB voting members receive and are expected to review the entire protocol package for all studies, not just the ones they are responsible for reviewing. All members receive the same information. Primary reviewers do not receive additional materials.

## 3.12 Criteria for IRB Approval of Research

The IRB shall determine the following during the initial and continuing review approval of research, as stated in the VA, DHHS, and FDA regulations.

In order for the IRB to approve human subjects research it must determine that the following requirements are satisfied (Section 111 criteria):

1. Risks to subjects are minimized: a) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and b) by using procedures already being performed on the subjects for diagnostic or treatment purposes, whenever appropriate.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment the IRB must take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving categories of populations who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative LAR, in accordance with, and to the extent required by 38 CFR 16.116.

5. Informed consent will be appropriately documented or appropriately waived, in accordance with, 38 CFR 16.117.

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

NOTE: 2018 Common Rule provides for limited IRB approval of certain categories of Exempt research.

### 3.12.1 Risks to Subjects

Per federal regulations, (38 CFR 16.111), the IRB must consider the overall level of risk to subjects in evaluating proposed research during the initial and continuing review of the research. The IRB identifies the risks to the subject. These risks are clearly identified in the research plan and the informed consent form. The IRB determines the level of risk of a protocol by evaluating the nature of several types of risk, including but not limited to physical, psychological, social, legal, and economic harms that could result from participation in the research. The IRB also evaluates the probability of the occurrence of a risk, as well as the severity of each potential risk in order to qualify each protocol as minimal or greater than minimal risk. The IRB determines the interval for continuing review based on the level of risk of the research project. The regulations require that the IRB distinguish research that is greater than minimal risk from research that is not greater than minimal risk, when considering proposals for expedited review and for vulnerable populations. However, the IRB assesses the risk/benefit ratio in all research protocols. During the time of the continuing review, the IRB determines that the risk level of the research has not changed since the initial approval.

The IRB uses the following criteria as per VA regulations at 38 CFR 16.102(i), for determining whether or not the risks to the subjects are minimal:

“**Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Generally, research projects that may be considered greater than minimal risk involve invasive procedures, a Phase I, II, III clinical trial, investigational drugs, or a significant risk investigational device.

### 3.11.2 Minimization of Risks

Per federal regulations, (38 CFR 16.111(a)(1)), to approve research, the IRB must determine at the time of initial and continuing review that risks are minimized by using procedures that are consistent with sound research design and which do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures that are already being performed on the subjects for diagnostic or treatment purposes.

The IRB examines the research plan, including research design and methodology, to

determine that there are no obvious flaws that would place subjects at unnecessary risk. This includes the risk that the research is so poorly designed or is so lacking in statistical power that meaningful results cannot be obtained.

The IRB also considers the professional qualifications of the PI and the study staff. The PI must designate all study staff in the protocol. The PI must have expertise in the relevant medical specialty being studied. The PI is in charge of: a) all patient safety issues related to the laboratory/study testing in the research, b) following all laboratory/study results and communicating all moderate or severe results to the study participant, the study participant's primary care and specialty physicians, and c) assuring the accurate recording of all relevant laboratory/studies in the patient's electronic medical record. The PI assumes ultimate responsibility for the conduct of the research and must have a paid VA appointment.

Clinicians are expected to maintain appropriate professional credentials and licensing privileges. The IRB reserves the right to request additional information from investigators and participating physicians to assure that the qualifications of the study staff are appropriate for the proposed study.

The Research Office Staff verifies that the individuals listed in the protocol have completed the appropriate credentialing and educational requirements consistent with HRPP Policy.

### 3.12.3 Reasonable Risk/Benefit Relationship

Per federal regulations (38 CFR 16.111(a)(2)) to approve research, the IRB must determine at the time of initial and continuing review that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects, and the importance of the knowledge that may reasonably be expected to result. This is also determined on an ongoing basis for other paperwork (such as amendments) submitted for each protocol. The IRB considers the following types of risks: physical, psychological, social, legal, and economic and determines the level of risks of the research. Probable individual and societal benefits of the research are also considered.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB should consider only those risks that result from the research, and should not consider the long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

### 3.12.4 Equitable Subject Selection

Per federal regulations, (38 CFR 16.111(a)(3)), the IRB determines by viewing the protocol and other research project materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. This is the concept of “justice” from the Belmont Report. In making this determination, the IRB evaluates: a) the purposes of the research; b) the

setting in which the research occurs; c) the scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons; d) the scientific and ethical justification for excluding classes of persons who might benefit from the research; and e) the inclusion/exclusion criteria.

At the time of the continuing review, the IRB will determine that the PI has followed the subject selection criteria that he/she originally set forth at the time of the initial IRB review and approval.

### 3.12.5 Informed Consent Requirements

To approve research, the IRB must determine that legally effective informed consent will be sought from each prospective subject or the subject's legally authorized representative (as per 38 CFR 16.116), unless informed consent requirements can be waived or altered under VA regulations. All informed consent forms and any such waivers must be consistent with applicable state laws regarding content and participation in research. Informed consent may only be sought under circumstances that: a) provide the subject (or the legally authorized representative) with sufficient opportunity to consider whether or not to participate; and b) minimize the possibility of coercion or undue influence (38CFR16.116). See Section 6 for a detailed discussion of informed consent requirements.

### 3.12.6 Informed Consent Documentation

The IRB will determine that informed consent is appropriately documented, unless documentation can be waived under VA regulations, the Common Rule, or FDA regulations. VA regulations at 38 CFR 16.117, the Common Rule, and FDA regulations provide two methods for documenting informed consent. See Section 5 for a detailed discussion of the requirements for documenting informed consent.

### 3.12.7 Review of Plans for Data and Safety Monitoring

Per federal regulations (38 CFR 16.111 (a)(6)), to approve research, the IRB determines that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of subjects. For all research that is more than minimal risk, the investigator must submit a data and safety monitoring plan. This plan should contain procedures for reporting adverse events (AEs). In general, it is desirable for a DSMB to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the funding agencies require a DSMB. When it determines that such monitoring is needed, the IRB has the authority to require a DSMB as a condition for approval of research. When DSMBs are utilized, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has and will continue to review study-wide AEs, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB.

The IRB determines that the safety monitoring plan makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of

subjects. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study. The method and degree of monitoring needed is related to the degree of risk involved. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator in a small, low risk study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. For an individual Safety Monitor the plan must include:
    - Parameters to be assessed
    - Mechanism to assess the critical efficacy endpoints at intervals in order to determine when to continue, modify, or stop a study.
    - Frequency of monitoring
    - Procedures for reporting to the IRB
5. For a Data Safety Monitoring Board, the plan must include:
    - The name of the Data Safety Monitoring Board
    - Where appropriate, is an independent from the sponsor
    - Availability of written reports
    - Composition of the monitoring group (if a group is to be used): experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.
    - Frequency and content of meeting reports
    - The frequency and character of monitoring meetings (e.g., open or closed, public or private)

### 3.12.8 Privacy of Subjects and Confidentiality of Data

Per federal regulations, (38 CFR 16.111 (a)(7)), the IRB along with input by the ISSO and PO will determine whether adequate procedures are in place to protect the privacy

of subjects and to maintain the confidentiality of the data.

### 3.12.8.1 Privacy

The IRB must determine whether the activities in the research constitute an invasion of privacy. In order to make that determination, the IRB must obtain information regarding how the investigators are accessing subjects or subjects' information and the subjects expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

Privacy refers to a person's desire to control the access of others to themselves. For example, persons may not want to be seen entering a place that might stigmatize them, such as a pregnancy counseling center that is clearly identified as such by signs on the front of the building. Privacy concerns people, whereas confidentiality concerns data. The research proposal should outline strategies to protect privacy including how the investigator will access information from or about participants.

In developing strategies for the protection of subjects' privacy, consideration should be given to:

- Methods used to identify and contact potential participants
- Settings in which an individual will be interacting with an investigator
- Appropriateness of all personnel present for research activities
- Methods used to obtain information about participants and the nature of the requested information
- Information that is obtained about individuals other than the "target participants," and whether such individuals meet the regulatory definition of "human participant" (e.g., a subject provides information about a family member for a survey)
- How to access the minimum amount of information necessary to complete the study.

### 3.12.8.2 Confidentiality

Confidentiality and anonymity are not the same. If anyone, including the investigator, can readily ascertain the identity of the subjects from the data, then the research is not anonymous and the IRB must determine if appropriate protections are in place to minimize the likelihood that the information will be inappropriately divulged. The level of confidentiality protections should be commensurate with the potential of harm from inappropriate disclosure.

At the time of initial review, the IRB assesses whether there are adequate provisions in place to ensure that the privacy and confidentiality of research subjects is protected. The IRB does this through the evaluation of the methods used to obtain information:

1. About subjects,
2. About individuals who may be recruited to participate in studies
3. The use of personally identifiable records and

4. The methods to protect the confidentiality of research data.

In some cases, the IRB may also require that a Certificate of Confidentiality (CoC) be obtained from Department of Health and Human Services (DHHS) to additionally protect research data

The PI will provide the information regarding the privacy and confidentiality of research subjects at the time of initial review through the completion of the application, any necessary HIPAA Forms, research protocol, and/or other submitted, applicable materials. The IRB will review all information received from the PI and determine whether or not the privacy and confidentiality of research subjects is sufficiently protected. The IRB primary reviewers will complete the IRB Reviewer Checklist at the time of initial review documenting such determinations.

In reviewing confidentiality protections, the IRB shall consider the nature, probability, and magnitude of harms that would be likely to result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed de-identification techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

The ISSO and PO review research projects that involve the use of veterans' data or another person's data and assesses the mechanisms in place to ensure security, confidentiality, release, and control of data derived from research subjects is in compliance with VHA policies and procedures.

The IRB serves as the Privacy Board for human subjects research at the VANEOHS and abides by the HIPAA Privacy Rule of 1996 and Section 12 of this document. The IRB recognizes the importance of protecting subject confidentiality, and carefully evaluates each protocol for the confidentiality measures taken. Only those authorized by the IRB shall be allowed access to individually identifiable patient information. Individuals must have prior approval by the IRB before receiving individually identifiable patient data for research purposes. This may include requiring such measures as a set of research codes, rather than the use of individually identifiable information, linked to the patient through only one codebook maintained by the PI.

### 3.11.9 Vulnerable Subjects and Safeguards Taken for Their Protection

Veteran patients/subjects who are economically dependent upon the VA for medical treatment, suffer from cognitive affective, or other psychological afflictions, or have substance abuse problems, may be particularly vulnerable to unintended, coercive or undue influences relative to participation in research. Likewise, persons who primarily utilize the VA facilities for treatment of their medical problems may not fully understand the implications of research participation, especially when it is offered by someone they consider a provider of clinical care.

The IRB must be cognizant of the vulnerable nature of many veteran patients/subjects. However, veterans are not as a whole considered a vulnerable population.

At the time of initial review the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. The IRB may determine and require that, when appropriate, additional safeguards be put into place for vulnerable subjects, such as those without decision-making capacity.

## 3.13 Considerations during IRB Review and Approval of Research

### 3.13.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research protocols. Risks associated with the research will be classified as either “minimal” or “greater than minimal”. The meeting minutes will reflect the IRB’s determination regarding risk levels.

### 3.13.2 Period of Approval

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research protocols. Protocols requiring continuing review will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, the IRB may require a shorter review interval (e.g. semiannually, quarterly, or after accrual of a specific number of participants). The meeting minutes will reflect the IRB’s determination regarding frequency of review.

For research subject to the 2018 requirements that meet one of the following categories, continuing review is not required.

- Research eligible for expedited review
- Research that has progressed to the point that it involves only one or both of the following, which are part of an IRB-approved study:
    - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
    - Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care
- Research reviewed by the IRB in accordance with the Limited IRB review provisions

#### 3.13.2.1 Review More Often Than Annually

Unless specifically waived by the IRB, research that meets any of the following criteria will require review more often than annually:

1. Significant risk to research subjects (e.g., death, permanent or long lasting disability or morbidity, severe toxicity) without the possibility of direct benefit to the subjects;
2. The involvement of especially vulnerable populations likely to be subject to coercion (e.g., terminally ill)

3. A history of serious or continuing noncompliance on the part of the PI.

The following factors will also be considered when determining which studies require review more frequently than on an annual basis:

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical condition of the proposed subjects.
3. The overall qualifications of the PI and other members of the study staff.
4. The specific experience of the PI and other members of the study staff in conducting similar research.
5. The nature and frequency of adverse events observed in similar research at this and other institutions.
6. The novelty of the research making unanticipated adverse events more likely.
7. Any other factors that the IRB deems relevant.

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects either studied or enrolled. If a maximum number of subjects studied or enrolled is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects studied or enrolled determines the approval period only when that number of subjects is studied or enrolled in less than one year.

### 3.13.3 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator such as by an audit may be necessary at times, for example, in cooperative studies, or other multi-center research. The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

1. Protocols where concerns, about possible material changes occurring without IRB approval, have been raised based on information provided in continuing review reports or from other sources.
2. Protocols conducted by PIs who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
3. Protocols randomly selected for internal audit.
4. Whenever else the IRB deems verification from outside sources is relevant.

The following factors will also be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.

2. The likely medical condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review, review of amendments, and/or adverse events.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

### 3.13.4 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

### 3.13.5 Investigator/Co-Investigator Conflicts of Interest

Investigators (PI and Co-I) are required to submit a “Conflict of Interest Assessment Form” at initial review, continuing review, and if any changes occur during the approval period. If an investigator or Co-Investigator responds affirmatively to the existence of a potential conflict, the COI Administrator is sent the form to make determinations. If a conflict of interest exists, final IRB approval of a protocol cannot be given until an approved conflict of interest management plan, that adequately protects the human subjects in the protocol, is in place.

### 3.13.6 Significant New Findings

During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. The PI must report any significant new findings to the IRB who will review them with regard to the impact on the subjects’ rights and welfare. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the IRB may require, during the ongoing review process, that the PI contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this to the PI. The informed consent must be updated and the IRB may require that the currently enrolled subjects be re-consented, acknowledging receipt of this new information and for affirming their continued participation.

### 3.13.7 Advertisements

The IRB must approve any and all advertisements prior to posting and/or distribution for studies that are conducted under the auspices of the VANEOHS. The IRB will review:

1. The information contained in the advertisement.
2. The mode of its communication.
3. The final copy of printed advertisements.
4. The final audio/video taped advertisements.

This information should be submitted to the IRB with the initial application or as an addendum to the protocol.

The IRB reviews to assure that the material is accurate and is not unduly optimistic, creating undue influence on the subject to participate. unduly optimistic language may include but is not limited to:

1. Statements implying a certainty of favorable outcomes or other benefits beyond what are outlined in the consent document and the protocol.
2. Claims, either explicitly or implicitly, that the drug, biologic, or device is safe or effective for the purposes under investigation.
3. Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device.
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article is investigational.
5. Promising “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation.
6. Emphasis on payment or the amount to be paid, such as bold type or larger font on printed media.
7. The inclusion of exculpatory/harsh language.

Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included:

1. The name and address of the investigator and/or research facility.
2. The condition being studied and/or the purpose of the research.
3. In summary form, the criteria that will be used to determine eligibility for the study.
4. The time or other commitment required of the subjects.
5. The location of the research and the person or office to contact for further information.
6. A clear statement that this is research and not treatment.
7. A brief list of potential benefits.

### 3.13.8 Recruitment Incentives

The VA does not allow any recruitment incentives (such as finder's fees and bonus payments) for investigators, study staff, physicians, and other health care providers for identifying and/or enrolling subjects or referring potential subjects for studies that are conducted under the auspices of the VANEOHS.

### 3.13.9 Payment to Research Subjects

Per federal regulations, (VHA Handbook 1200.05), at the time of initial application, the IRB reviews any financial or other form of payment to research subjects to assure that the amount does not create an undue influence on the subject to participate. The information is provided in the protocol and the consent form. Additional information may be required on an "as needed" basis.

Payments may not be provided to subjects on a schedule that results in undue influence on the subject's decision to continue participation. Payment may not be withheld as a condition of the subject completing the research. Any amount paid as bonus for completion of the entire study should not be so great that it creates undue influence. If the subject withdraws early, payment must be prorated to reflect the time and inconvenience of the subject's participation up to that point. The schedule, amount, and conditions of payment must be stated in the informed consent form.

VA policy prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care.

Compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing is prohibited.

However, payment may be permitted, with prior approval of the IRB, in the following circumstances:

1. **No direct subject benefit.** When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this same or similar situation.
2. **Others being paid.** In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same proposed rate, the IRB may find that payment is appropriate.
3. **Comparable situations.** In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.
4. **Transportation Expenses.** When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are reimbursed by another mechanism.

Investigators who wish to pay research subjects must indicate in their research project

application the justification for such payment.

The R&D Committee must ensure that such payments to subjects are made from appropriate funds.

For specific procedures for paying research volunteers see Medical Research Service policies HSP-008A “Paying Human Subject Volunteers with VA Appropriated Funds” and HSP-008B “Paying Human Subject Volunteers with Research Foundation Administered Funds.”

### 3.13.10 Compensation for Research Related Injuries

Per federal regulations, (38CFR16.116 (a)(6) and 38 CFR 17.85), information on compensation for injury must be included in all informed consent forms. It must include contact names and telephone numbers, per the required elements of informed consent.

VA medical facilities shall provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by the R&D Committee and conducted under the supervision of one or more VA employees.

However, this requirement does not apply to:

1. Treatment for injuries due to a subject’s noncompliance with study procedures;
2. Research conducted for the VA under a contract with an individual or a non-VA institution.

For additional information, regarding exceptions to this information, please see 38 CFR 17.85.

For sponsored research, VANEOHS requires the use of the local research related injury boilerplate language in the informed consent form instead of the sponsor’s compensation statement. The VA policy for research-related injuries provides very broad coverage, more than what most sponsors provide. The contract between the institution and the sponsor will define those instances when the sponsor will provide compensation.

### 3.13.11 Certificates of Confidentiality (CoC)

Generally, any Federally-funded research project that involves the use or collection of identifiable, sensitive information will be required to have a Certificate of Confidentiality as required by Section 2012 of the 21st Century Cures Act (42 U.S.C. 241). For purposes of this section and as defined in the 21st Century Cures Act, the term identifiable, sensitive information means information about an individual that is gathered or used during the course of research in which an individual is identified; or there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual. An investigator issued a certificate must protect the privacy of individuals involved in the research study and may not disclose or provide to any other person not connected with

the research the name of subjects or any information, document, or biospecimen that contains identifiable, sensitive information about subjects that was created or compiled for purposes of the research.

Disclosure of identifiable information outside of the research team is prohibited, except:

(1) When there is a Federal, State or local law requiring disclosure of information, such as for reporting child or elder abuse or communicable diseases;

(2) When the subject consents for such disclosure;

(3) For medical treatment of the individual made with consent of the subject; or

(4) When the information is used for other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

When VA conducts a study that is protected by a Certificate of Confidentiality, the following requirements apply:

(1) For studies in which information about the subject's participation will be included in the subject's VHA medical record, information must be given to the prospective subjects as part of the informed consent process that information regarding study participation will be included in the medical record; and

(2) For studies in which the IRB requires a written informed consent, the informed consent document approved by the IRB must include a statement that the study has a Certificate of Confidentiality. NOTE: The HHS agencies that issue Certificates of Confidentiality usually have guidance specific to the issuing agency on statements that must be included in informed consent documents describing Certificates of Confidentiality.

As of June 13, 2017, all previously issued Certificates of Confidentiality are subject to the requirements of Section 2012 of the 21st Century Cures Act,

For studies not funded by DHHS, if there is an IND or an IDE, the sponsor can request a CoC from the FDA.

### 3.13.12 Compliance with all Applicable State and Local Laws

The IRB follows and must adhere to all applicable state and local laws in the jurisdictions where the research is taking place. The Research Service and the IRB rely on the Regional Counsel for the interpretation and application of Ohio State law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. All consent forms must be consistent with applicable state and local laws.

Currently there are no Ohio statutes that conflict with or enhance federal requirements on research done at federal facilities. If Ohio law is amended to require more stringent

regulations than are currently required in the federal regulations, the policy is to follow the more stringent state requirements.

### 3.12.13 Participation of Non-Veterans as Research Subjects

The investigator must provide justification for including non-Veterans in a VA research protocol, and the R&DC must review the justification for inclusion of non-Veterans and specifically approve entering non-Veterans into the study before any non-Veterans can be recruited.

a. Outpatient Care for Research Purposes. Any person who is a bona fide volunteer may be furnished outpatient treatment when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.92).

b. Hospital Care for Research Purposes. Any person who is a bona fide volunteer may be admitted to a VA hospital when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR 17.45).

c. Other Research. Non-Veterans may be entered into an approved VA research study when the investigator can present a compelling argument for the inclusion of non-Veterans (e.g., insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members), and the research is relevant to the care of Veterans or active duty military personnel.

d. Investigators must provide notice of privacy practices to any non-veteran enrolled in an approved VA protocol

See Medical Research Service policy **HSP-004 "CPRS Medical Records for Non-Veteran Research Subjects and Veterans not Currently Enrolled in the VA system**" for entering subjects into the Computerized Patient Record System (CPRS).

### 3.12.14 Researcher Contact with Veterans

1. Researchers must restrict their telephone and other contacts with veterans to only those procedures and data elements outlined in IRB approved protocols. In these contacts, researchers must not request social security numbers.
2. During the recruitment process, researchers must make initial contacts with veterans in person and/or by letter prior to any telephone contact and provide a telephone number or other means that veterans can use to verify the validity of the study. One source of information about clinical trials that can be shared with veteran is http://www.clinicaltrials.gov/ where VA clinical trials are listed.
3. Informed consent documents must include information about where and how a veteran can verify the validity of a study and authorized contacts.
4. After recruitment and during the follow-up phase, a researcher should begin calls by referring to previous contacts and the information provided on the informed

consent document

### 3.12.15 Study Closures

Upon completion of the research project, the IRB reviews and may approve or acknowledge and accept study closures upon receipt of the “Study Closure Report” and applicable documents from the investigator. It should be noted that a study is not considered “closed” if there is ongoing analysis of individually identifiable data.

### 3.12.16 Documentation in the Medical Health Record

A VHA health record is created or updated, and a progress note created, for all research subjects (Veterans or Non-Veterans) who are admitted to VA facilities as inpatients, treated as outpatients at VA facilities, or when research procedures or interventions are used in the medical care of the VA research subject at a VA facility or at facilities contracted by VA to provide services to Veterans. See HSP-003, “Documentation in the Patient’s Health Record of Research Enrollment, Contact, Actual Enrollment and End of Study Participation.”

### 3.12.17 Flagging Of the Electronic Medical Record

Research studies that the IRB recognizes as greater than minimal risk may require that a research flag be activated in the patient’s CPRS electronic medical record for the safety of the subject. An electronic record flag advisory is an electronic record flag, which serves as an immediately identifiable alert that promotes safe, appropriate, timely, and respectful patient care. The VA electronic medical record is programmed such that when patients with electronic record flags make scheduled or unscheduled visits to the medical center and clinics, the patient information display will show a screen with the established type of flag advisory highlight. See Medical Research Service HSP-005 “Flagging Medical Charts of Patients Involved in Medical Research Studies” for information for the process of activating, managing, and removing a research flag.

Studies that generally require a flag are those that are invasive, including studies requiring surgery and/or utilizing investigational drugs or significant risk investigational devices as well as other interventions or clinical services used in the medical care of the subject or that could interfere with the subject’s other medical care. The IRB may also require flagging for surveys that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interests of the subject (e.g., an interview study of victims of sexual assault). In other situations, the IRB determines if flagging is necessary Flags may also be applied to studies for which the IRB considers it important that any medical staff member working with an enrolled patient knows that he/she is participating in a research study.

The IRB study approval letter will notify the PI and study coordinator that the IRB determined that a research flag is required for all study subjects.

As patients are enrolled into the research protocol, the PI will obtain a signed informed consent and enter the patient’s name into the medical record flag advisory system. The PI is responsible for activating the research flag immediately following the informed consent process with a patient. The investigator is responsible for deactivating the

research flag if a patient withdraws or participation ends prior to the termination of the study and for de-activating the research protocol flag when the study is concluded.

A patient may be enrolled in only one research study for which the IRB has required a flag advisory in the patient's electronic medical records. The IRB Co-Chairperson must approve any exceptions in advance.

The IRB may not want to require the medical record to be flagged or may consider lifting the flagging requirement if:

1. The subject's participation in the study involves:
    a. Only one encounter,
    b. Only the use of a questionnaire, or
    c. The use of previously collected biological specimens.
2. The identification of the patient as a subject in a particular study (if the study is not greater than minimal risk) would place the subject at greater than minimal risk.

## 3.13 Possible IRB Actions

**Approved** with no changes (or no additional changes).

**Approvable with modifications**: The protocol requires minor modifications and/or revisions before approval can be given. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. When the revisions are received from the investigator, the IRB Co-Chairperson, or another experienced IRB member designated by the Chairperson, may review and approve the revised research protocol under expedited procedures on behalf of the IRB. The date of approval is the date when the minor changes were approved by the reviewer. The research may not begin until the reviewer has approved the changes and the R&D Committee has performed an activation review and approved the research and the PI receives a notification of approval form the ACOS/R&D. The approval by the reviewer must be documented in the minutes of the first IRB meeting that takes place after the date of the approval.

**Deferred**. The IRB determines that substantial modification or clarification of the protocol is required, or insufficient information is provided to adequately judge the protocol application. The research approval process may not proceed until the convened IRB has approved a revised application incorporating necessary information.

**Disapproved.** The IRB has determined that the research cannot be conducted at this VA or by employees or agents of the VANEOHS or otherwise under the auspices of the VA.

**Suspension/Termination**. The IRB may suspend or terminate approval of active research due to investigator noncompliance, unexpected problems, or serious harm to subjects.

**Tabled.** A study tabled by the IRB is a study that was not reviewed. The IRB may table a

study if the IRB did not have sufficient time, expertise, or appropriate personnel present (i.e., absence of primary reviewer) to vote on the study or for investigator noncompliance.

**Approval in Principle.** As per federal regulations, (38CFR16.118), there are two circumstances in which the IRB may grant approval required by a sponsoring agency without having reviewed all of the study procedures and consent documents.

1. One is if study procedures are to be developed during the course of the research, but human subjects approval is required by the sponsoring agency.

2. The other is if the involvement of human subjects depends on the outcomes of work with animal subjects. The IRB may then grant approval without having reviewed the as yet undeveloped recruitment, consent, and intervention materials. However, if the proposal is funded, the Principal Investigator must submit such materials for approval at least 60 days before recruiting human subjects into the study, or into any pilot studies or pre-tests.

Approval in principle is granted to satisfy sponsoring agency requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects.

## 3.14 Study Suspension, Termination and Investigator Hold

### 3.14.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. See Section 6 for a discussion of unexpected problems.

**Suspension** of IRB approval is a directive of the convened IRB or IRB Co-Chairperson to temporarily stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspension directives made by the IRB Co-Chairperson must be reported to a meeting of the convened IRB. Suspended protocols remain open and require continuing review. Suspensions by the IRB Co-Chairperson will be reported to the IRB for review.

**Termination** of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review. Terminations of protocols approved under expedited review must be made by the convened IRB.

The IRB shall notify the PI in writing of such suspensions or terminations and shall include a statement of the reasons for the IRB's actions. The terms and conditions of the suspension or termination must be explicit. The investigator shall be provided with an opportunity to respond in person or in writing.

When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual

ordering the suspension or termination will assure any subjects currently participating are notified that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled subjects are necessary to protect their rights and welfare of subjects, such as: transferring participants to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of participants for safety reasons.

If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require that the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

The investigator MUST continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsor just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period.)

In addition to the IRB and or Co-Chairperson, the COS may suspend research if the immediate well-being of patients participating in research is compromised. In such cases, the COS will notify the IRB Co-Chairperson and the ACOS/R&D. The IRB will be notified of these actions at the next convened meeting.

It is the responsibility of the IRB Co-Chairperson and/or the ACOS/R&D to provide prompt written notification to the R&D Committee, the COS (where appropriate) and the medical center Director as well as to relevant federal agencies, including ORO, OHRP, and FDA (for FDA-regulated research) of suspensions and terminations (e.g. associated with unexpected harm and research not being conducted in accordance with the IRB's requirements) of IRB approved research projects. Routine study closures, expirations in IRB approvals, or study completions are not required to be reported to these agencies.]

### 3.14.2 Investigator Hold

An investigator may request an Investigator Hold on a protocol when he/she wishes to temporarily or permanently stop some or all approved research activities. An investigator hold is initiated by an investigator. Investigator holds are not suspensions or terminations. The term Investigator Hold does not apply to interruptions of VA research related to concerns regarding the safety, rights, or welfare of human research subjects, research investigators, research staff or others. An investigator hold must not be used to avoid reporting deficiencies or circumstance otherwise covered by VA Handbooks or other Federal Requirements governing research.

#### 3.14.2.1 Procedures

1. Written notification to the IRB from the investigators must include:
    a. A statement that he/she is placing a study on administrative hold voluntarily or in response to a request by the convened IRB or IRB designee.

b. A description of the research activities that will be stopped.

c. Proposed actions to be taken to protect current participants.

d. Actions that will be taken, prior to IRB approval of proposed changes, in order to eliminate apparent immediate harm.

2. Upon receipt of this written notification, the IRB Administrator places the research on the agenda for review.

3. The IRB Co-Chairperson, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants.

4. The IRB Co-Chairperson, in consultation with the investigator, determines how and when currently enrolled participants will be notified of the investigator hold.

5. The investigator may request a modification of the Investigator Hold by submitting a Request for Modification to Previously Approved Research Form.

## 3.15 Initial Review

### 3.15.1 Initial Review Materials

The materials required for submission for all new (initial) protocols can be found in VAIRRS/IRBnet.

3.16.2 Initial IRB Review Process

1. **Review of the research protocol:** The information received from the investigator will be reviewed by the IRB to determine if the research project meets the criteria for approval. The reviewers should complete the IRB Reviewer Checklist to document that each of the specific criteria for approval has been met. The IRB Reviewer Checklist will be filed in the IRB study file in the IRB office.
2. **Review of the Informed Consent form:** The IRB will review and determine that all required elements are included in the consent process and any required consent forms.
3. **Review of the Request for Waiver of Documentation or Alteration of Consent:** The IRB will review requests for waivers of informed consent and waivers of documentation of informed consent. The IRB will determine if the request meets the necessary requirements and this determination will be documented in the minutes.
4. **Review of Request for Waiver of Authorization for the Use of Protected Health Information for Research Purposes**: The IRB will review requests for waiver of authorization for the use of protected health information for research purposes. The IRB will determine if the request meets the necessary requirements and this determination will be documented in the minutes.

5. **Review of Conflict of Interest:** If an investigator or study staff responds affirmatively to the existence of a potential conflict of interest, the COI Administrator will be notified. The COI Administrator will review the disclosure and determine whether an actual conflict exists. A written memorandum providing information concerning the COI will be provided to the IRB. The IRB will review this information and will determine a management plan that adequately protects the human subjects in the protocol is in place.
6. **Payment to Subjects:** The IRB will determine whether proposed payments to subjects comply with VHA policy are appropriate and do not represent undue influence on potential subjects.
7. **Recruitment Incentives:** The VA does not allow any recruitment incentives for investigators, study staff, physicians, and other health care providers for identifying and/or enrolling subjects or referring potential subjects for studies that are conducted under the auspices of this VA.
8. **Advertisements and Recruitment Methods:** IRB members will review the content of all proposed recruitment methods, submitted protocol advertisements, and all other written material to be provided to subjects. The primary reviewer will evaluate the materials for appropriateness, assuring that the advertisements do not represent an undue influence or coercion for potential research participants and that they are clear and understandable for the potential research participants under study.
9. **Review of Safety Monitoring:** For studies that are blinded, have multiple sites, recruit vulnerable populations, or employ high-risk interventions or treatments, a general description of the data and safety monitoring plan must be submitted to the IRB as part of the proposed work. This plan should contain procedures, for identification and reporting of adverse events. For studies that have a DSMB, the research plan must make adequate provisions for monitoring the data collected to ensure the safety of the subjects. Additionally, all research, including those that have the potential for using biohazardous agents, are reviewed by the SRS. This review occurs concurrently with the IRB review process. The specific requirements for submission to the SRS are outlined in medical center policy 151-007 “Subcommittee on Research Safety.”
10. **Investigational Drug Support and Investigational Drug Records:** The R&D Committee will determine that the investigator has made appropriate arrangements for providing monetary support to the Research Pharmacy for the cost of storing and dispensing drugs and keeping pharmacy logs. The IRB will assure that there is a VA Form 10-9012 Investigational Drug Information Record for all investigational drugs, including placebos, and FDA marketed drugs used in a potential research study. The Research Pharmacist is a voting member of the IRB, so this is an additional safeguard to assure compliance with this requirement.
11. **PI Response to Contingent Approvals:** When minor modifications are required the PI is notified in writing of the specific revisions that the IRB has requested. The IRB Co-Chairperson and/or primary reviewer(s) and/or designee will review minor modifications, and once it has been determined that they are in

compliance with IRB recommendations, will advise the IRB Administrator or Staff, who will create an approval letter.

If an investigator does not respond to the IRB stipulations within about a three-month period, the IRB office will contact the investigator and inquire about his/her intentions regarding the study. If the PI is unresponsive to this request, then the IRB may determine to administratively withdraw the study from consideration, at which point the PI must resubmit the study anew for R&D Committee and IRB review. The IRB will consider exceptions to this policy in extraordinary circumstances that may be out of the investigator's control. These circumstances may include: awaiting confirmation regarding funding status; or awaiting changes being made by the sponsor, which may extend the time that an investigator needs to make required modifications.

## 3.16 Continuing Review

For studies requiring continuing review, the IRB will conduct the review at intervals that are appropriate to the level of risk for each research protocol, but not less than once per year. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur even when the remaining research activities are limited to the analysis of private identifiable information.

For research subject to the 2018 Requirements, unless the IRB determines otherwise, continuing review is not required in the following circumstances:

(a) Research eligible for expedited review; or

(b) Research reviewed by the IRB in accordance with the limited IRB review; or

(c) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

1. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

2. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

(3) For research subject to the 2018 Requirements, if the IRB requires continuing review for any of the above circumstances, it must document its rationale for requiring continuing review in its communication to the investigator and institution. The R&D Committee is not required to conduct continuing review for studies approved by the IRB for which continuing review by the IRB is not required.

***NOTE:*** *Research not requiring continuing review by an IRB is still overseen by the IRB. Reportable events, such as unanticipated problems involving risks to subjects or others,*

*must be reported as required by the IRB. Any changes in the IRB-approved research must be reported to the IRB and may not be implemented prior to review and approval by the IRB (may be expedited) except when necessary to eliminate apparent immediate hazards to the subject.*

### 3.16.1 Continuing Review Materials

The materials required for submission for all continuing reviews (progress reports) are outlined below:

1. Continuing Review Form that includes a status report of the research, the number of subjects enrolled to date, any new findings, any subjects withdrawn and the reasons for withdrawal, a summary of serious adverse events occurring within the continuing review period, a summary of unanticipated problems involving risks to subjects and/or others, investigator risk/potential benefit assessment based upon the study results, complaints about the research, a summary of any modifications and or amendments to the research, any interim findings, any relevant literature findings, audit reports and any other information that would impact the IRBs review of the research.
2. Investigator's brochure, if applicable.
3. Data Safety Monitoring reports, if any.
4. Any other documents relevant to the continuing review of research.

### Non-Reportable Events

All events, problems, and new information that do not meet reporting requirements must be reported to the IRB in summary form at the time of the next continuing review.

The IRB recognizes that sponsors may require that the PI report all serious adverse events and IND safety reports to the IRB. The IRB complies with this request in an efficient manner to acknowledge receipt of these reports.

PIs should report adverse events and IND safety reports that do not meet the reporting requirements by using the Tracking Log for Non-Reportable Events form.

Upon receipt, the IRB Administrative Staff will review the Tracking Log for Non-Reportable Events and check the form for completeness. The form will be returned to the investigator if incomplete.

If the investigator answers yes to all three of the questions for a specific event, the investigator is required to complete an Unanticipated Event Reporting form.

Otherwise, the IRB Administrative Staff will acknowledge receipt by the IRB, sign and date the form, and return a copy of the form to the PI.

### 3.16.2 Approval Period

At VANEOHS, determination of the approval period and the need for additional supervision and/or participation is made by the IRB on a protocol-by-protocol basis. For example, for an investigator who is performing particularly risky research, or for an investigator who has recently had a protocol suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee of the IRB might occur or approval might be subject to an audit of study performance after a few months of enrollment, or after enrollment of the first several subjects.

For each initial or continuing approval the IRB will indicate an approval period with an approval expiration date specified. IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a study approved by the convened IRB, the approval period starts on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB approved the research or the date the convened IRB deferred the research for non-substantive issues. For a study approved under expedited review, the approval period begins on the date the IRB Co-Chairperson or IRB member(s) designated by the Chairperson gives final approval to the protocol.

The approval date and approval expiration date are clearly noted on all IRB correspondence sent to the PI and must be strictly adhered to. Investigators should allow sufficient time for development and review of renewal submissions.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur by midnight of the date when IRB approval expires. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

### 3.16.3 Continuing Review Process

During the continuing review process, the IRB evaluates the following for appropriateness and any necessary follow-up:

1. That the research still meets the IRB review criteria for approval.
2. Any changes to the research.
3. Number of subjects entered and withdrawn (including the reason for withdrawal) for the review period and since the inception of the research project.
4. Adverse event reports, safety reports, including IND, IDE and MedWatch reports summarized for the IRB.
5. A summary of DSMB or DMC meeting reports (if applicable) or any findings based on information collected by the data and safety monitoring plan submitted in the initial proposal.

6. Any unanticipated problems and complaints regarding the research.

7. Summary of new participant benefits identified over the continuing review period.

8. Protocol violation/deviation reports.

9. Any significant, new findings that have occurred since the initial or previous review. This includes new scientific findings in literature, or other relevant findings that may impact on the research.

10. Overall investigator noncompliance with IRB requirements for frequency of periodic continuing review.

In conducting continuing review of research not eligible for expedited review, all IRB members are provided and review all of the material noted above in and the primary reviewer(s) will review the complete protocol, including any modifications previously approved by the IRB. At the meeting, the primary reviewer(s) lead the IRB through the completion of the regulatory criteria for approval in the Continuing Review Reviewer Checklist.

The IRB Administrative Staff attends the convened meetings.

In the case of expedited review, the IRB members may request the IRB office staff to provide them with any additional materials required for the review.

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

### 3.16.4 Expedited Review of Continuing Review

In conducting continuing review under expedited review, reviewers review materials in VAIRRS/IRBNet. The Reviewer will complete the “Continuing Review Reviewer Checklist” to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367. It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

### 3.16.5 When There is a Lapse in Continuing Review

The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired, is research conducted

without IRB approval. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (advertisements must be stopped or removed from public view), enrollment, consent, interventions, interactions, data collection, and data analysis. The IRB staff notifies the investigator of the expiration of approval and that all research activities must stop.

If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval, the PI must immediately submit to the IRB Co-Chairperson a list of research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects can only continue when the IRB or IRB Co-Chairperson, in consultation with the COS, finds that it is in the best interest of the individual subjects to do so.

In determining the appropriate course of action for FDA-regulated studies, the COS and IRB Co-Chairperson must follow appropriate federal regulations (21 CFR 56.108(b)(3)). The sponsoring agency, private sponsor, ORD, ORO or other federal agencies must be informed of the lapse of approval, as appropriate.

Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research. If the study approval has lapsed more than 45 days and the PI has not provided the required continuing review information, the PI must submit a new application, through the R&D Committee, to the IRB for review and approval. If the study approval has lapsed 45 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

If a research protocol receives contingent approval at the time of the continuing review and the approval expires before the PI responds to the contingencies, the PI may not enroll any new subjects or access medical records after the approval expiration date. Once the PI responds, the existing protocol will be reviewed for continuation. If the PI does not respond for an extended period, the IRB may vote to administratively close the study. Decisions of this kind must be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing treatment as part of the research study.

Once the PI submits the required information, it will be reviewed as appropriate by the IRB. Failure to submit continuing review information on time is noncompliance and will be handled according to the noncompliance policy. This will be evaluated on a case-by-case basis.

Research Status Updates

For studies that do not require continuing review by the IRB, investigators are required to provide an annual update on the status research using the IRB Status Report. Responses that indicate that the study should be closed will prompt a request for the PI to submit a study closure report. Investigators failing to respond will be re-contacted

once the suspense date has passed for an update.

## 3.17 Protocol Revisions, Modifications, and Amendments of an Approved Protocol

### 3.17.1 Protocol Modifications, and Amendments Materials

Investigators must submit documentation to inform the IRB about the changes in the status of the study.

### 3.17.2 Protocol Revisions, Modifications, and Amendments Process

Investigators may wish to amend their approved applications. Investigators must obtain IRB approval before making any changes in approved research - even though the changes are planned for the period for which IRB approval has already been given - unless the change is necessary to eliminate an immediate hazard to the subject (in which case the PI must notify the IRB within 5 working days of making said changes).

Amendments may be approved if they are within the scope of what the IRB originally authorized. For example, if a researcher wishes to add a population to an existing study, but not alter the study procedures or purpose, an amendment request is usually appropriate. Likewise, modifying a procedure without changing the study's purpose or study population may also be appropriate. If, however, the researcher wishes to make substantial changes to the study procedures, he or she will need to submit a new application for human subjects approval.

Investigators must submit the required documentation to inform the IRB about the proposed changes in the protocol. A request for expedited review of the proposed changes may be requested by the PI on the IRB modification forms, and the IRB Administrative Staff will make the initial determination as to whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the amendment warrants full board review. The IRB reviews all materials received in the review of modifications to an approved protocol.

#### 3.17.2.1 Expedited review of Protocol Amendments

An IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized [38 CFR 16.110 and 21 CFR 56.110(b)]. An expedited review may be carried out by the IRB Co-Chairperson or by one or more experienced reviewers designated by the IRB Co-Chairperson from among the voting members of the IRB. If the reviewer determines that the change is not minor, then the protocol will be referred for full IRB review.

#### 3.17.2.2 Full Board Review of Protocol Amendments

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the

proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare. The primary reviewers that were assigned at initial review of the study will review all protocol amendments throughout the life of the study.

When the IRB reviews amendments to previously approved research, the IRB considers whether information about those amendments might relate to participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

## 3.18 Notifications of IRB Review

It is the responsibility of the IRB to make all of the appropriate notifications to all of the required individuals and committees within a reasonable time following the convened IRB meeting. The IRB Administrator and/or IRB Analyst generate the written notifications for approvals prior to review by the IRB Co-Chairperson or his/her designee. The IRB Administrator and/or IRB Analyst generate written correspondence for contingent approvals and/or deferral notifications. The IRB Co-Chairperson or designee may review IRB correspondence prior to sending the notification to the investigator.

The ultimate responsibility for these timely notifications rests with the IRB Co-Chairperson and the IRB Administrator.

The necessary notifications are as follows:

1. **Notification to the investigator.** The IRB will notify the PI in writing of its determinations and the need for any additional information or action, usually within 5-10 business days after the convened IRB meeting. The notification includes approvals, approvals with modifications, deferrals, disapprovals, suspensions, terminations, or tabled protocols. In the case of a suspension, there must be a clear, explicit reason for the IRB action. The PI will be afforded the opportunity to respond to the IRB's decision in writing or in person.

2. **Notification to the R&D Committee**. The IRB will notify the R&D Committee in writing of its actions pertaining to all items reviewed at the convened IRB through the IRB meeting minutes, which also include decisions about expedited and exempt reviews. Additionally, it is the responsibility of the IRB to notify the R&D Committee in writing about for-cause suspensions, terminations of IRB approved research projects, any serious unanticipated problems involving risk to subjects or others and the anticipated resolution of these problems.

3. **Notification to the Chief of Staff**. The IRB will notify the COS, through the ACOS/R&D, in writing about for-cause suspensions and any serious unanticipated problems involving risk to subjects and others and the anticipated resolution of the problem.

**4. Notification to the Medical Center Director.** The IRB Chair or designee will notify the Director in writing, within 5 business days if the convened IRB or qualified IRB member-reviewer determines that a reported problem or event is serious and unanticipated and related to the research,

Within 5 business days of determining that a reported incident constitutes serious noncompliance or continuing noncompliance, the IRB Chair or designee must report the determination directly (without intermediaries) to the facility Director.

Within 5 business days, any termination or suspension of research related to concerns about the safety, rights, or welfare of human research subjects, research staff, or others, must be reported directly (without intermediaries) to the facility Director.

## 3.19 Appeal of IRB Decisions

When an IRB protocol discussed at a convened meeting is not approved as presented, the IRB will notify the PI in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval.

## Chapter 4 Documentation and Records

## 4.1 Purpose

The VANEOHS shall prepare and maintain adequate documentation of the IRB's activities. All records must be accessible for inspection and copying by authorized representatives of the FDA, OHRP, sponsors, and other authorized entities at reasonable times and in a reasonable manner.

## 4.2 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures.
2. IRB membership rosters,
3. IRB correspondence (other than protocol related).
4. IRB Study Files
5. Documentation of Emergency Exemption from Prospective IRB Approval. (21 CFR 56.104(c)).
6. Documentation of Exceptions from Informed Consent Requirements for Emergency Use of a Test Article ((21 CFR 50.23).
7. Documentation of exemptions
8. Documentation of convened IRB meetings minutes
9. Documentation of review by another institution's IRB when appropriate.
10. Documentation of cooperative review agreements, e.g. Memoranda of Understanding (MOUs).
11. Federal Wide Assurances.
12. Protocol violations submitted to the IRB
13. Quality assurance reviews.

## 4.3 IRB Study Files

For new studies submitted through VAIRRS/IRBNet, all documentation/files are maintained within that system.

Paper files are maintained for pre VAIRRS/IRBnet approvals.

**PAPER FILES**

Protocols will be assigned a unique identification number by the IRB Administrative Staff and entered into the IRB tracking system.

Accurate records are maintained of all communications to and from the IRB. Copies are filed either in the Principal Investigator's project file or electronic file. The VANEOHS IRB maintains a separate file for each research protocol that includes, but is not limited to:

1. Protocol and all other documents submitted as part of a new protocol application.
2. Protocol and all other documents submitted as part of a request for continuing review/termination of research application. This also includes progress reports, statements of significant new findings provided to participants, reports of injuries to patients.
3. Documents submitted and reviewed after the study has been approved, including reports of modifications to research/amendments and adverse event reports.
4. Copy of IRB-approved Consent Form
5. DHHS-approved sample consent form document and protocol, when they exist
6. IRB reviewer checklists Documentation of type of IRB review.
7. For expedited review, documentation of any determinations required by the regulations and protocol-specific findings supporting those determinations, including: waiver or alteration of the consent process, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children.
8. Documentation of all IRB review actions.
9. Notification of expiration of IRB approval to the PI and instructions for submitting relevant continuing review materials.
10. Notification of suspension of research.
11. Correspondence pertaining to appeals.
12. Copies of approval letters and forms that describe what Principal Investigator must have before beginning the study.
13. IRB correspondence to and from research investigators.
14. All other IRB correspondence related to the research.
15. For devices, a report of prior investigations.
16. Reports of unanticipated problems involving risk to subjects or others and adverse events.
17. Documentation of audits, investigations, reports of external site visits.

## 4.4 IRB Membership Roster

A membership list of IRB members must be maintained; it must identify members sufficiently to describe each member's chief anticipated contributions to IRB deliberations. The list must contain the following information about members:

1. Name
2. Earned degrees
3. Affiliated or non-affiliated status (neither the member nor an immediate family member may be affiliated with the university)
4. Status as scientist (physician-scientist, other scientist, non-scientist or social behavioral scientist) or non-scientist. For purposes of this roster, IRB members with research experience are designated as scientists. Students being trained in research

fields will be designated as scientists. Research experience includes training in research (e.g., doctoral degrees with a research-based thesis) and previous or current conduct of research.
5. Indications of experience, such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; which IRB member is a prisoner representative (as required by Subpart C) (please note that the VANEOHS does not conduct research involving prisoners).
7. Role on the IRB (Chairperson, etc.)
8. Voting status (Any *ex officio* members are non-voting)
9. Alternate status, including the member they alternate with
10. Relationship (e.g., employment) between the individual IRB member and this VA.

The IRB Administrator ensures that current IRB membership rosters are maintained and any changes in IRB membership are reported promptly by the IRB Administrator to OHRP through ORO.

## 4.8 The IRB Minutes

The IRB Administrator compiles the minutes of IRB meetings. The following specific information is recorded in the meeting minutes:

1. Attendance
    a. Names of members present
    b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that all received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions
    c. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members only as designated on the official IRB membership roster)
    d. Names of consultants present
    e. Name of investigators present
    f. Names of guests present

    Note: The initial attendance list shall include all members that were in attendance during the entire meeting. The minutes will indicate, by name, those members who leave during a specific agenda item vote. The vote on each action will reflect those members present for the vote on that item.
2. The presence of a quorum throughout the meeting, including the presence of one member whose primary concern is in a non-scientific area
3. Business items discussed

4. Continuing education

5. Actions taken, including separate deliberations, actions, and votes for each protocol undergoing review by the convened IRB.

6. Votes on these actions (Total Number Voting; Non-Scientists; Number voting for; opposed; abstaining; recused)

7. Basis or justification for these actions including required changes in research

8. Basis for disapproving research

9. Summary of controverted issues and their resolution

10. Approval period for initial and continuing approved protocols, including identification of research that warrants review more often than annually and the basis for that determination

11. Risk level of initial and continuing approved protocols

12. Review of interim reports, e.g. unanticipated problems, amendments, report of violation/deviations, etc.

13. Review of Data and Safety Monitoring Board (DSMB) summary

14. Review of Plans for Data and Safety Monitoring

15. Applications that have met or not met the stipulations for approval

16. Protocol-specific documentation that the research meets the required criteria (38 CFR 16.116(d)) when approving a consent procedure that does not include or that alters some or all of the required elements of informed consent, or when waiving the requirement to obtain an informed consent

17. Protocol-specific documentation that the research meets the required criteria [38 CFR 16.117(c)] when the requirements for documentation of consent are waived

18. When approving research that involves populations covered by Subparts B, C, or D of 45 CFR 46, the minutes will document the IRB's justifications and findings regarding the determinations stated in the Subparts, or the IRB's agreement with the findings and justifications as presented by the investigator on the IRB forms

19. When approving a Request for Waiver or Alteration of Authorization to use and/or Disclose Protected Health Information in Research the minutes will document the IRB's justifications and findings that determine the criteria set forth in subparagraph 4.B.(1) are met.

20. The rationale for significant risk/non-significant risk device determinations

21. The Conflict of Interest Administrator's determinations of conflict of interest and any IRB required action plan.

22. Justification of any deletion or substantive modification of information concerning of risks or alternative procedures contained in the DHHS-approved sample consent document.

23. Identification of any research for which there is need for verification from sources

other than the investigator that no material changes are made in the research (e.g., Cooperative Studies, or other collaborative research)

24. Protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research. See Section 6 “Vulnerable Subjects in Research” for information on vulnerable subjects.
25. A list of research approved by expedited review procedures and the specific citation for the category of expedited review of the individual protocol.
26. Documentation of approval by the Co-Chairperson or designee of research contingent on specific minor conditions in the minutes of the first IRB meeting that takes place after the date of the approval.
27. An indication that, when an IRB member has a conflicting interest with the research under re view, the IRB member was not present during the deliberations or voting on the proposal, and that the quorum was maintained.
28. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant

Minutes will be written and prepared usually within three weeks of the meeting date and made available for review. After the minutes have been reviewed and approved by the convened IRB, the IRB Administrator forwards a copy of the IRB meeting minutes to the R&D Committee Coordinator for R&D Committee review and acknowledgement. The IRB minutes, once approved, may not be altered by any persons of authority except by the IRB Co-Chairperson with the concurrence and approval of the convened IRB.

IRB minutes, through the review of R&D Committee minutes, are made available to the medical center Director. Approved IRB minutes are maintained in the IRB Offices by the IRB Administrator.

## 4.9 Record Retention

IRB records are to be retained in accordance with VHA’s Records Control Schedule (RCS 10-1).

Current IRB study files, study files pending IRB approval, study files completed in the previous year, and IRB records not associated with study files are stored in the IRB VA Offices, K-122, under the supervision of the IRB Administrative Staff.

All other study files are stored in the local record storage area per medical center policy 136-011 “Records Management.”

Investigators maintain their own study files and ensure the security and confidentiality of data records. In the event an investigator leaves the VA facility; original research records

must be maintained at the VANEOHS.

## Chapter 5 Obtaining Informed Consent from Research Subjects

## 5.1 Purpose

No investigator may involve a human being as a subject in research without obtaining the legally effective informed consent of the subject or the subject's legally authorized representative unless a waiver of consent has been approved by the IRB in accordance with Section 5.8 and Section 5.9 of these procedures. Except as provided in Section 5.8 and Section 5.9 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

If someone other than the PI conducts the interview and obtains consent from a patient, the PI needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study.

See Section 6.9.4 (Persons with Impaired Decision-Making) for the requirement for surrogate consent.

*These informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for informed consent to be legally effective.*

The following procedures describe the requirements for obtaining consent from participants in research conducted under the auspices of VANEOHS.

## 5.2 Definitions

**Legally Authorized Representative**. A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this policy, a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older) or a close friend.

**Legal guardian**. A person appointed by a court of appropriate jurisdiction.

**Case History**. A case history is a record of all observations and other data pertinent to the investigation on each research subject. The PI is required to prepare and maintain adequate and accurate case histories. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including, but are not limited to: progress notes of the physician, the individual's hospital

chart(s), and nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

## 5.3 Informed Consent Process

When applicable, an investigator using human subjects as part of the proposed study must submit a Research Consent Form. All consent forms must have approval by the IRB and R&D committees prior to use. Approval is documented by a stamp of IRB approval.

VA regulations under 38 CFR 16.116, the Common Rule, and FDA regulations require that informed consent be obtained under the following circumstances:

1. Informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

2. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, consent must be obtained from a legal guardian or a legally authorized representative.

3. The informed consent process shall be sought under circumstances that provide the subject (or legally authorized representative) with sufficient opportunity to consider whether or not to participate and, should minimize the possibility of coercion or undue influence.

4. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.

5. The informed consent information must be presented in language that is understandable to the subject (or legally authorized representative). To the extent possible, the language should be understandable by a person who is educated at the $6^{th}$ to $8^{th}$ grade level. Layman's terms and simple sentences shall be used in the description of the research.

6. The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of his/her legal rights or through which the investigator, the sponsor, the VANEOHS or VA employees or agents are released, or appear to be released, from liability for negligence.

7. The PI is responsible for insuring that each prospective subject is adequately informed about all aspects of the research.

8. For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent. The VANEOHS has a Limited English Proficiency (LEP) Program available that assists in obtaining translators for veterans who do not speak English. See medical center policy 003-007 "Limited English Proficiency (LEP) Title VI Prohibition against

National Origin Discrimination in Federally Conducted Programs and Activities." For more information about the LEP program contact Patient Care Administrative Services at (216) 791-3800 ext. 7300 and ask for the LEP Coordinator.

## 5.4 Basic Elements of Informed Consent (38 CFR 16.116)

1. The name of the study and the name of the PI.
2. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;
3. A description of any reasonably foreseeable risks or discomforts to the subject;
4. A description of any benefits to the subject or to others that may reasonably be expected from the research;
5. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
6. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
7. An explanation as to whether any compensation is available, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
8. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject; and
9. A statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
10. A statement about any research that involves the collection of identifiable private information or identifiable biospecimens: (a) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the LAR, if this might be a possibility; or (b) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.
11. A statement that VA will provide treatment for research related injury in accordance with 38 CFR 17.85 (see section 24 of this directive). NOTE: VA's statutory requirements in 38 CFR 17.85 apply regardless of inclusion of the information as part of the informed consent process.

    For all research studies including sponsored research, the VANEOHS requires the use of the local research related injury boilerplate language in the informed consent form:

    The VA policy for research-related injuries provides very broad coverage, more than what most sponsors provide. The contract between the institution and the sponsor will define those instances when the sponsor will provide

compensation.

**NOTE:** VA regulations on research related injuries (see 38 CFR 17.85) apply to minimal-risk research also.

a. The regulation at 38 CFR 17.85 does not apply to research conducted for VA under a contract with an individual or a non-VA institution (although veterans injured as a result of participation in such research may nevertheless be eligible for care from VA under other statutory and regulatory provisions). Information on the responsibility for research-related injury under such circumstances must be included in the consent form. **NOTE:** It is strongly suggested that the investigator make provisions for coverage of such cost in research awards and contracts.

### 5.4.1 Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject or LAR:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or becomes pregnant) that are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the LAR's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly and safe termination of participation by the subject;
5. A statement that any significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;
6. The approximate number of subjects to be entered in the study;
7. If there is a sponsor, the sponsor name and number of participating sites
8. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
9. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
10. For studies involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen); and
11. When appropriate, a statement that informs VA research subjects that they or their insurance will not be charged for any costs related to the research. NOTE: Some Veterans are required to pay copayments for medical care and services specifically related to their medical care provided by VA. These co-payment

requirements will continue to apply to medical care and services that are not part of the research procedures or interventions.

## 5.5 Documentation of Informed Consent

Except as provided in Section 5.8 and Section 5.9 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

### 5.5.1 Consent Form Procedures

All elements of the informed consent form (ICF) are to be discussed with the study subject, allowing the subject sufficient time to decide whether or not he/she wants to participate in the study. The ICF may be mailed to subject prior to the first study visit. The PI and/or designee must discuss the ICF with the subject and address all questions within his/her scope of responsibility**.**

If a potential research participant is unable to give informed consent for him/her, his/her legally authorized representative may consent on behalf of him/her to participate in the procedure(s). See Section 6 for information related to vulnerable populations the obtaining surrogate consent from the legally authorized representative.

Prior to engaging in any study activities, subjects or the subject's legally authorized representative will sign and date the ICF. The ICF signed by the subject must be stamped.

If a separate HIPAA Authorization form is used, the PI and/or designee is also responsible for obtaining the signature authorizing the use of or disclosure of protected health information unless authorization requirements can be waived or altered under the HIPAA Privacy Rule.

The PI and/or designee ensure documentation of the consent process in the subject's medical record. Documentation must be entered as a research note in CPRS. Refer to Medical Research Policy HSP–003 "Documentation in Patient's Medical Record of Enrollment Contact, Actual Enrollment and End of Study Participation."

The original signed consent document must be filed in the subject's case history (study file), which is maintained by the PI.

A copy of the signed and dated ICF must be provided to the study subject or to the subject's legal representative. (VHA Handbook 1200.05).

If the research study meets the requirements for documentation in the VHA health record (SOP HSP-003), VHA regulation requires a copy of the signed and dated Informed Consent Document and signed and dated HIPPA authorization be place in the medical record. See also, SOP HSP-020, Scanning Research Documentation.

For research studies involving investigational drugs, a copy of the signed and dated consent form must be provided to the Research Pharmacist prior to dispensing any study medications.

If during the course of the study, the protocol is amended - i.e. the risks/benefit ratio of study, procedures, payment to subjects – which may affect the subject's willingness to continue participating in the study, the consent form must be revised to reflect changes. The revised ICF must be submitted to the VANEOHS IRB for review and approval. After IRB review and approval of the revised ICF, the IRB approval date of the revision will be indicated on the IRB approved consent stamp.

Study participants (or the subject's legally authorized representative) must be re-consented when the ICF revisions could affect their willingness to participate in the study.

It is very important for study staff members to keep in mind that informed consent is a process, not something obtained simply by having a prospective participant sign a consent form. And getting a participant's signature on the consent form does not end the process. The study staff must keep participants informed of any significant new findings developed during the study that may affect their willingness to continue in the study. Informed consent is a legal and moral responsibility to uphold the individual autonomy and personal dignity of all people who consider participating in research.

### 5.5.2 Required Signatures

A valid consent must be signed and dated by the following individuals the subject or his /her legally authorized representative

## 5.6 Special Consent Circumstances

### 5.6.1 Non-English Speaking Subjects

1. **Expected enrollment of non-English speaking subjects:** In some protocols, the PI expects non-English speaking subjects to enroll because, for example, the protocol is studying a disease or condition that is likely to attract them or the PI is actively recruiting them. When the study subject population includes non-English speaking people or the PI and/or the IRB anticipates that consent discussions will be conducted in a language other than English, the IRB shall require a translated consent document to be prepared. In order to assure itself that the translation is accurate, the IRB may choose to require a certified translation, to have an independent back translation or to have a review of the consent document by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and the witness sign the translated document. The subjects are given a copy of the signed translated consent document.

2. **Unexpected enrollment of a non-English speaking subject:** If a non-English speaking subject is unexpectedly eligible for protocol enrollment, there may not be an existing IRB-approved written translation of the consent document. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly

understand the information presented at the signing of the consent document or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

If a PI decides to enroll a subject into a protocol for which there is not an extant IRB-approved informed consent document in the prospective subject's language, the PI must follow the procedures for oral consent as described in Section 5.6.3. The person obtaining consent must document that the oral consent process was used in the progress notes of the subject's medical record.

3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to deliver information in the IRB-approved script and to facilitate the consent conversation. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the IRB-approved consent form well before (24 to 48 hours if possible) the consent conversation with the subject. If the interpreter also serves as the witness, she/he may sign the consent document as the witness and should note "Interpreter" under the signature line. The person obtaining consent must document that the oral consent process was used in the progress notes of the subject's medical record, including the name of the interpreter.

### 5.6.2 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise verbal consent will be obtained, witnessed and documented as described below.

### 5.6.3 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 5.9.

## 5.7 Consent Monitoring

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that special monitoring of the consent process by an impartial observer (consent monitor) is required in order to reduce the possibility of coercion and undue influence, ensure that the approved consent process is being

followed, or ensure that subjects are truly giving informed consent.

Such monitoring may be particularly warranted for:

- Greater than minimal risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving highly vulnerable populations (e.g., ICU patients, children)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or
- Other situations when the IRB has concerns that the consent process is not being conducted appropriately.

Monitoring may also be appropriate as a corrective action when the IRB has identified problems associated with a particular investigator or a research project.

If the IRB determines that consent monitoring is required, the IRB Co-Chairperson and the IRB Administrator will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring may be conducted by the IRB Administrator, IRB members or another party, either affiliated or not affiliated with the institution. The PI will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the PI for the monitoring of the consent process for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately completed and documented,
- Whether the participant had sufficient time to consider study participation,
- Whether the consent process involved coercion or undue influence,
- Whether the information was accurate and conveyed in understandable language, and
- Whether the subject appeared to understand the information and gave their voluntary consent.

Following the monitoring, a report of the findings will be submitted to the IRB, which will determine the appropriate action to be taken.

## 5.8 Waiver of Informed Consent

As defined in 38 CFR 16.116(c) an IRB may 1) approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or 2) waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs
    b. Procedures for obtaining benefits or services under those programs

c. Possible changes in or alternatives to those programs or procedures; or

d. Possible changes in methods or levels of payment for benefits or services under those programs.

e. The research could not practicably be carried out without the waiver or alteration.

An IRB may 1) approve a consent procedure that omits some, or that alters some or all of the elements of informed consent set forth above; or 2) waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects must be provided with additional pertinent information after participation.

FDA regulations do not provide for waivers of informed consent except in emergency situations.

## 5.9 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either that the:

1. Only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, and the research is not FDA-regulated, or only record linking the subject and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, or

   **Note 1:** Subjects must be asked whether they want documentation linking them with the research, and their wishes must govern. (Example: domestic violence research where the primary risk is discovery by the abuser that the subject is talking to researchers.)

   **Note 2:** In order to waive written documentation of consent where the only record linking the participant and the research would be the consent document, the IRB has to determine that the research was not FDA-regulated.

2. Research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-researchers.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject. The IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

## Chapter 6 Vulnerable Subjects in Research

## 6.1 Purpose

When some or all of the participants in a research conducted under the auspices of VANEOHS are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

The following procedures describe the requirements for involving vulnerable participants in research under the auspices of VANEOHS.

## 67.2 Definitions

**Surrogate Consent** is consent obtained from a legally authorized representative on behalf of a participant determined to lack decision-making capacity.

**Legally Authorized Representative**. A legally authorized representative is defined as an individual, or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research in the following descending order of priority:

1. Person appointed as healthcare agents under DPAHC
2. Court-appointed guardian of the other person
3. Spouse
4. Adult child 18 years of age or older
5. Parent
6. Adult siblings
7. Grandparent
8. Adult grandchild
9. A non-related person who is documented in the medical record for having capacity to make decisions on behalf of the intended subject

The preceding list contains the surrogate entities allowed to provide consent for research purposes. Refusal to consent by a person who is a higher priority surrogate shall not be superseded by a person who is a lower priority surrogate. Additionally, if there are two or more individuals in the same class, the decision must be unanimous to provide consent.

**Consent Assessor** is a researcher or consultant familiar with dementias and qualified to assess and monitor capacity to consent on an ongoing basis.

**Prisoner** is any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals: 1) sentenced to such an institution under a criminal or civil statute, 2) detained in other facilities by virtue of statutes or commitment

procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, or 3) detained pending arraignment, trial, or sentencing (please note that the VANEOHS does not conduct research involving prisoners).

**Children** are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. Ohio Revised Code Section 4109.01 defines a “minor” as “any person less than 18 years of age.” Ohio does not have an emancipation of minors statute or definition (Ohio courts do recognize minors as “emancipated” in certain circumstances, but that is only in a case-by-case basis). Therefore, the VANEOHS IRB generally defines children as persons under eighteen years of age. For research conducted in jurisdictions other than Ohio, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The Regional Counsel will provide assistance with regard to the laws in other jurisdictions.

**Assent** means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

**Permission** means the agreement of parent(s) or guardian to the participation of their child or ward in research.

**Parent** means a child's biological or adoptive parent.

**Guardian** means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care. For research conducted in jurisdictions other than Ohio, the research must comply with the laws regarding the legal age of consent in all relevant jurisdictions. The Regional Counsel will provide assistance with regard to the laws in other jurisdictions.

**Pregnancy** is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until delivery of the fetus.

**Delivery** means complete separation of the fetus from the woman by expulsion, extraction, or any other means.

**Fetus** is the product of conception from the time of implantation until delivery.

**Viable fetus** is now termed a “viable neonate.”

**Nonviable fetus** is a fetus ex utero that, although living, is not able to survive to the point of independently maintaining heart and respiration. ***NOTE:*** *In 45 CFR 46 Subpart B, this definition is used as the definition of a non-viable neonate.*

**Dead fetus** is a fetus which exhibits neither heartbeat, spontaneous respiratory activity,

spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

**In vitro fertilization** is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

**Neonate** means newborn.

**Viable neonate** means being able after delivery to survive to the point of being independently maintaining heart and respiration (given the benefit of available medical therapy).

**Non-viable neonate** means the same as a non-viable fetus

## 6.3 Involvement of Vulnerable Populations

Vulnerable populations involved in research as listed in the federal regulations include pregnant women and fetuses, prisoners, mentally disabled and those with impaired decision-making capacity, children, and economically and educationally disadvantaged persons. The VANEOHS does not conduct research involving prisoners; or, if the subject is a fetus, in-utero or ex-utero (including human fetal tissue); or any research related to in vitro fertilization. Cleveland City Ordinance 231.05 prohibits any experimentation or selling of fetal tissue which is the result of an abortion.

The VANEOHS further recognizes VA employees and volunteers may be subject to undue influence and are thus potentially vulnerable to coercion. For research involving the participation of children as research subjects, the IRB must determine that the proposed research meets the requirements outlined in VHA Handbook 1200.05. For research involving the participation of pregnant women as research subjects, the IRB must determine that the proposed research meets the requirements outlined in VHA Handbook 1200.05.

The IRB shall adhere to the guidance regarding the use of vulnerable populations in research as defined in Title 38 Code of Federal Regulations (CFR) 16.111(b) and the VHA Handbook 1200.05.

## 6.4 Responsibilities

1. The PI is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal. He/she is responsible for identifying subjects who are at risk for impaired decisional capacity and who are being asked to participate in a research study that poses greater than minimal risk.
2. The IRB shall include representation, either as voting members or consultants, by individual(s) interested in or who have experience with the vulnerable populations involved in a research proposal.
3. The IRB reviews the PI's justifications for including vulnerable populations in the research to assess its appropriateness.
4. At the time of initial review and at continuing review of the protocol, the IRB must

ensure that additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects as needed.

5. The IRB shall continue to review research at intervals appropriate to the degree of risk and determine whether the proposed research continues to fulfill criteria for approval. Information reviewed will include the number of participants considered as members of specific vulnerable populations.
6. For studies that do not have, or are not required to have, a DSMB or a Data Monitoring Committee, and have enrolled vulnerable subjects, the IRB will carefully review the data and safety monitoring plan. (VHA Handbook 1200.05.)

## 6.5 Procedures

1. Initial Review of Research Proposal:
    a. The PI completes required documents and identifies the potential to enroll vulnerable subjects in the proposed research and provides justification for their inclusion in the study. The investigator should include the procedure(s) that will used to determine the subject's capacity to provide voluntary informed consent to participate in research.
    b. The IRB evaluates the proposed plan for consent of the specific vulnerable subjects involved. If the research involves adults unable to consent, the IRB evaluates the proposed plan for permission of legally authorized representatives based on guidelines for research involving human subject with surrogate consent in VHA Handbook 1200.05.
    c. The PI should provide appropriate safeguards to protect the subject’s rights and welfare, which may include the addition of an independent monitor. The independent monitor may be a physician, psychologist or registered nurse not involved in the research study who will determine the subject’s capacity to provide voluntary informed consent to participate in research at intervals commensurate with the risk of the study.
    d. The IRB assess the adequacy of additional protections for vulnerable populations provided by the PI.
    e. The IRB evaluates and approves the proposed plan for the assent of participants.
    f. Examples of studies that may warrant independent monitoring include those involving patients with Serious Mental Illness (SMI), dementia, delirium, or other conditions that compromise ability to consent, or those who may be exposed to placebo, drug washout, and/or treatment with investigational agents that are not approved by the FDA. The investigator should include the plan for independent monitoring in the study protocol. The subject may need to be periodically reconsented to participate in the research. The plan should define who will make the determination to reconsent the subject and outline the process for ensuring that it is completed.
    g. If needed, the independent monitor will evaluate the subject prior to enrollment in the study to determine consent capacity.
2. Documentation, if the PI obtains an independent monitor to evaluate subjects with

impaired decision capacity.

a. An electronic progress note will document the independent monitor's evaluation and is included in the research subject file. The CPRS note will include the following:
    - Investigator name and study name and number
    - Brief patient summary
    - Patient's understanding of study and reason he/she was asked to participate
    - Understanding of risks
    - Understanding of right to decline study participation without penalty
    - Determination of relevant decision-making capacity.
b. The PI will ensure that the monitor has evaluated the subject prior to initiating any procedures or tests pertaining to the research study.
c. The independent monitor may withdraw research subjects from the study if the monitor determines that continued participation in the study is not in the volunteer's best interest.

3. At continuing review, the PI should identify the number of vulnerable subjects enrolled and any that needed an independent monitor in the progress report.
4. The IRB evaluates the research to determine the need for additional protections and considers the use of a DSMB or data monitoring committee as appropriate.
5. The PI will develop a monitoring plan that accounts for the need for heightened surveillance during periods of higher risk, e.g., during medication washout or periods of potential placebo treatment and schedule monitoring visits at intervals commensurate with the risk to human research volunteers.

## 6.6 Research Involving Pregnant Women, Human Fetuses and Neonates as Subjects

Research that involves provision of in vitro fertilization services can be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. This includes prospective and retrospective research involving provision of or the enhancement of FDA-approved methods of in vitro fertilization for studies involving consenting subjects, both male and female, undergoing or who have undergone in vitro fertilization for the treatment of certain forms of human infertility. In vitro fertilization is any fertilization of human ova that occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

Prospective and retrospective studies that enroll or include pregnant subjects who conceived through in vitro fertilization or other artificial reproductive technologies are permitted.

Research in which the focus is either a fetus, either in-utero or ex-utero can be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. Use of human fetal tissue (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-143.html and https://grants.nih.gov/grants/guide/notice-files/not-od-16-033.html) and human stem cells (https://stemcells.nih.gov/policy/2009-guidelines.htm) shall be governed by the policy set by NIH for recipients of NIH research funding.

Research involving the creation of a human embryo or embryos solely for research purposes or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498B of the Public Health Service Act (42 U.S.C. 289g(b)) cannot be conducted by VA Investigators, at VA facilities, or at VA approved off-site facilities.

Women who are known to be pregnant and their fetuses may be involved in research if all the following requirements are met and the VA medical facility Director certifies that the VA medical facility has sufficient expertise in women's or reproductive health to conduct the proposed research if the research includes interventional studies or invasive monitoring of pregnant women as subjects (see guidance at https://www.research.va.gov/resources/policies/default.cfm), including informed consent requirements and the following ethical and scientific criteria:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus. If there is no such prospect of benefit, then the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions outlined in this document;
5. Each individual providing consent under (2) or (4) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate
6. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
7. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
8. Individuals engaged in the research will have no part in determining the viability of a neonate.

VA investigators cannot conduct interventions in research that include neonates while on official VA duty, at VA facilities, or at VA-approved off-site facilities. VA investigators may conduct research involving noninvasive monitoring of neonates if the research is determined by the IRB to be minimal risk. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted.

The reviewing IRB must have the appropriate expertise to evaluate any VA research involving neonates and must comply with the requirements of 45 CFR 46.205. The VA medical facility Director must certify that the medical facility has sufficient expertise in neonatal health to conduct the proposed research.

For research involving the participation of pregnant women as research subjects, the IRB must determine:

- that the proposed research meets the requirements outlined in this document.
- that adequate provisions have been made to monitor the risks to the subject and the fetus.
- that adequate considerations have been given to the manner in which potential subjects will be selected, and that adequate provisions have been made to monitor the informed consent process such as:
    - Overseeing the process by which the consent of individuals is obtained either by:
        - Approving enrollment of each individual
        - Verifying, perhaps through sampling, that approved procedures for enrollment of individuals into the activity are being followed.
    - Monitoring the progress of the activity and intervening, as necessary, through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

**NOTE:** These determinations should be documented in the IRB Minutes. **General limitations:**

1. Activities related to pregnant women must not be undertaken unless:
    a. Appropriate studies on animals and non-pregnant individuals have been completed, and data for assessing potential risks to pregnant women and fetuses is provided.
    b. The purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal, and, in all cases, is the least possible risk for achieving the objectives of the activity.
    c. PI and study staff engaged in the activity will have no part in: i) any decisions as to the timing, method, and procedures used to: terminate the pregnancy; or ii) determining the viability of the fetus at the termination of the pregnancy, and/or iii) Introducing any procedural changes, for research purposes, into the procedures for terminating the pregnancy
2. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity.

3. No pregnant woman may be involved as a subject in a research activity unless:

   a. The purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or

   b. The risk to the fetus is minimal;

   c. The mother and father are legally competent and have given their informed consent to participate in the research after having been fully informed regarding possible impact on the fetus. The father's informed consent need not be secured if: i) the purpose of the activity is to meet the health needs of the mother, ii) his identity or whereabouts cannot reasonably be ascertained, iii) he is not reasonably available, or iv) the pregnancy resulted from rape.

## 6.7 Research Involving Prisoners as Subjects

Prisoners are considered a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether or not to participate as subjects in research. Therefore, research involving prisoners must not be conducted by VA investigators while on official duty, at VA Facilities or at VA-approved off-site facilities unless a waiver has been granted by the CRADO**.** Waiver requests must be submitted electronically to the CRADO by the VA medical facility Director.

When a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by the IRB in accordance with the requirements of HHS regulations at 45 CFR 46, subpart C, the PI should promptly notify the IRB and the R&D Office of this event. All research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.

If the PI wishes to have the prisoner subject continue to participate in the research, the R&D Office will request a waiver from the CRADO. Once the waiver is granted, the IRB should promptly re-review the protocol in accordance with the requirements of subpart C. In special circumstances in which the PI asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Co-Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

It is important that the IRB remind the PI that, except in the special circumstances noted above, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all of the requirements of subpart C have been satisfied with respect to the relevant protocol.

## 6.8 Research Involving Children as Research Subjects

The VA is authorized to care for veterans and to conduct research that supports the mission of VHA and that enhances the quality of health care delivery to veterans.

Therefore, research involving children must be reviewed carefully by the IRB for its relevance to VA and must not present greater than minimal risk to the children.

The VA medical facility Director must approve participation in the proposed research that includes children. The Research office can provide guidance for obtaining approval.

NOTE: For purposes of this directive, research involving biological specimens or data obtained from children is considered to be research involving children even if de-identified. If the biological specimens or data were previously collected, they must have been collected under applicable Federal policies and ethical guidelines.

The IRB must have the appropriate expertise to evaluate any VA research involving children and must comply with the requirements of 45 CFR 46.401 - 46.404 and 46.408.

***NOTE:*** *For purposes of this SOP, research involving children does not include neonates.*

### 6.8.1 Allowable Categories

The IRB must make certain findings and determinations when reviewing research involving children. IRB records must reflect the IRB's understanding and justification for the risks and benefits posed by approved research involving children. Proposed research must fall within one of the following four categories:

1. Research not involving physical or emotional risk greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (i.e., **minimal risk**). (45 CFR 46.404)
   The IRB may find that the permission of one parent is sufficient.

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. (45 CFR 46.405)
   - The risk is justified by the anticipated benefit to the subjects;
   - The IRB may find that the permission of one parent is sufficient;
   - Requires assent of the child.

3. Research involving greater than minimal risk and no reasonable prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR 46.406)
   - The risk represents a minor increase over minimal risk;
   - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   - Permission of either/or both parents - unless one parent is deceased, unknown, incompetent, or not reasonably available; or only one parent has legal responsibility for the care and custody of the child – or a legal guardian is required.
   - Requires assent of the child.

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children. (45 CFR 46.407)
    - Federally-funded research in this category must be approved by the Secretary of HHS, and requires consent of either/or both parents, or legal guardian.
    - For non-federally-funded research, the IRB will consult with a panel of experts in pertinent disciplines (e.g. science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on finding either:
        1. That the research in fact satisfies the conditions of the previous categories, as applicable; or
        2. The following:
            i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
            ii. The research will be conducted in accord with sound ethical principles; and
            iii. Informed consent will be obtained in accordance with the provisions for informed consent and other applicable sections of this SOP.

**6.8.2 Parental Permission and Assent 7.8.2.1 Parental Permission**

In accordance with 45 CFR 46.408(b) the IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent as stated in 45 CFR 46.116(a)(1-8) and any additional elements the IRB deems necessary.

The IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405. The IRB's determination of whether consent must be obtained from one or both parents will be documented in the consent checklist when a protocol receives expedited review, and in meeting minutes when reviewed by the convened committee.

Consent from both parents is required for research to be conducted under 45 CFR 46.406 and 45 CFR 46.407 unless:

- One parent is deceased, unknown, incompetent, or not reasonably available; or
- When only one parent has legal responsibility for the care and custody of the child.

The IRB may waive the requirement for obtaining consent from a parent or legal guardian if:

- The research does not involve an FDA-regulated product
- The research meets the provisions for waiver in 45 CFR 46.116(d)(1-4) and if the IRB determines that the research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children).
- An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and the waiver is not inconsistent with Federal State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by 45 CFR 46.117.

#### 6.8.2.2 Assent from Children

Because “assent” means a child’s affirmative agreement to participate in research, (45 CFR 46.402(b), the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve.

The IRB presumes that children ages 7 and older should be given an opportunity to provide assent. Generally, oral assent through the use of a script should be obtained from children 7 - 11 years of age. Written assent using a written document for the children to sign may be sought for older children.

At times there may be inconsistency between parental permission and child assent. Usually a "no" from the child overrides a "yes" from a parent, but a child typically cannot decide to be in research over the objections of a parent. Obviously, there are individual

exceptions to these guidelines (such as when the use of an experimental treatment for a life-threatening disease is being considered). The general idea, however, is that children should not be forced to be research subjects, even when their parents consent to it.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or wellbeing of the children, and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

Even when the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances detailed in the Waiver of Informed Consent section of this SOP.

**The Assent Form**

Researchers should draft a form that is age appropriate and study specific, takes into account the typical child's experience and level of understanding, and that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. tell why the research is being conducted;
2. describe what will happen and for how long or how often;
3. say it's up to the child to participate and that it's okay to say no;
4. explain if it will hurt and if so for how long and how often;
5. say what the child's other choices are;
6. describe any good things that might happen;
7. say whether there is any compensation for participating; and
8. ask for questions from the child.

For younger children, the document should be limited to one page if possible. Illustrations might be helpful, and larger type makes a form easier for young children to read. Studies involving older children or adolescents should include more information and may use more complex language.

### 6.8.2.3 Use of Consultants

When reviewing research proposed to include children as subjects, the IRB may call in consultants, e.g., pediatricians, child psychologists/psychiatrists, etc. who may be able to provide important consultation regarding the proposed research and any consent or assent concerns. In the event that an investigator plans to include children in a research study, the IRB usually selects consultants from one of our affiliated medical centers, such as University Hospitals Rainbow Babies & Children’s Hospitals. (See Section 3.10 “Use of Consultants.”)

### 6.8.2.4 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research involving greater than minimal risk and has no prospect of direct benefit to individual subjects, but is likely to yield generalizable knowledge about the subject's disorder or condition, **only if such research** is:

1. related to their status as wards; or
2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis (in place of a parent).*

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

## 6.9 Persons with Impaired Decision Making Capacity as a Vulnerable Population in Research

### 6.9.1 Research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

1. Only incompetent persons or persons with impaired decision-making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.

2. The proposed research entails no significant risks, tangible or intangible. However, if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

3. Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision-making capacity. Health care agents (DPAHC) and next-of-kin, or guardians, must be given descriptions of both proposed

research studies and their obligations as the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe the subject may not be capable of making voluntary and informed decisions about research participation. This may be determined either by implementing into the research procedures a method for determining decision-making capability, or it may be determined by consulting existing medical records where a qualified practitioner has recorded decision-making capability. The IRB may require the use of professionals and methods to assess capacity to give consent. If the reason for lack of capacity is because of mental illness, then a psychiatrist or licensed psychologist must confirm this judgement and document it in the individual's medical record as a signed and dated progress note.

When it is determined that a potential research subject is not capable of making a voluntary and informed decision about research participation, a legally authorized representative may consent on behalf of the individual.

### 6.9.2 Determination of Decision-Making Capacity

The decision-making capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation.

The investigator and study staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent.
For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group.
For research that poses greater than minimal risk, the IRB may require investigators to use independent and qualified professionals to assess whether potential subjects have the capacity to give voluntary, informed consent. Even in research involving only minimal risk, the IRB may require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision making capacity, the IRB may require that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and

consenting process or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairment to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measures might include: 1) follow-up questions to assess the subject's understanding, 2) videotaping or audio-taping consent interviews, 3) soliciting second opinions, 4) use of independent consent observers, 5) use of an interpreter for hearing-impaired subjects, 6) allowing a waiting period before enrollment, or 7) involving a trusted family member or friend in the disclosure and decision making process.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For those subjects or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

In the event research participants become incompetent or impaired in decision making capacity after enrollment, the PI is responsible for notifying the IRB and R&D Office. The PI is responsible for developing a monitoring plan which follows the guidelines outlined above for incompetent and impaired decision making research participants.

#### 6.9.2.1 Determining Capacity to Consent

Decisional capacity in the research context has been interpreted by the American Psychiatric Association (APA) as requiring:

- Ability to evidence a choice,
- Ability to understand relevant information,
- Ability to appreciate the situation and its likely consequences, and
- Ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity to give consent. In general, the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity to consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he/she is sufficiently independent of the study staff and/or institution.

The majority of studies conducted at the LSCVAMC only allow enrolling subjects who have the capacity to consent. For studies that have been approved for enrolling vulnerable populations who may lack capacity to consent, there must be someone who is able to assess the capacity of each potential subject to consent. If the PI makes the initial

judgment that the potential subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time, then this must be confirmed in consultation with the Service Chief or COS. Additionally, if the reason for lack of capacity is because of mental illness, then a psychiatrist or licensed psychologist must confirm this judgment and document it in the individual's medical record as a signed and dated progress note.

A person, who has been determined to lack capacity to consent to participate in a research study; must be informed of this determination before permission may be sought from his/her legally authorized representative to enroll that person in the study. If permission is given to enroll such a person in the study, the potential subject must then be informed. If the potential subject indicates that he/she does not wish to participate then the surrogate consent cannot be honored.

### 6.9.3 Informed Consent and Assent

Whenever feasible, persons with impaired decision-making should be given an assent form that has the required basic components of a research consent form. Assent for participation from impaired adults will be sought and any objections/concerns regarding participation or their desire to withdraw from the research study will be respected.

A person who is incompetent or has been determined to lack capacity to consent to participate in a research study should be informed about the trial to the extent compatible with the subject's understanding and, if possible, the subject should give their assent to participate, sign and date the written informed consent or a separate assent form. If the potential subject indicates that he/she does not wish to participate then the surrogate consent cannot be honored.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects a re-consenting process with surrogate consent may be necessary. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

### 6.9.4 Surrogate Consent

VA's General Counsel has determined that the "applicable law" to be used in determining the appropriate surrogate is VA's Informed Consent statute (38 U.S.C. 7331) and its Informed Consent Regulation (38 CFR 17.32). [VAOPGCADV 7-2005]. Regional Counsel has advised, "VA would not look to Ohio State law in determining the appropriate surrogate for consent to research.

If it has been verified that the potential research participant is unable to give informed consent for him/herself, his/her legally authorized representative may consent on behalf of him/her to participate in the procedure(s). A legally authorized representative is defined

as an individual, or judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research in the following descending order of priority:

- Person appointed as healthcare agents under DPAHC
- Court appointed guardian of the person
- Spouse
- Adult child (8 years of age or older)
- Parent
- Adult siblings (18 years of age or older)
- Grandparent
- Adult grandchild (18 years of age or older)

Please Note: The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes. Refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate. Additionally, if there are two or more individuals in the same class and the decision is not unanimous among all available members of the class, then no person under this section may provide informed consent. Surrogates may not receive financial compensation for providing the consent.

A surrogate must be fully informed of the study and have sufficient opportunity to consider what the wishes of the potential subject would be and whether or not to consent on behalf of the subject. The surrogate must receive all of the information a regular enrollee would receive in language that is understandable to the surrogate. Surrogate consent will be accepted in the order identified in the SOP and consistent with Ohio state law. If the potential subject indicates that he/she does not wish to participate then the surrogate consent cannot be honored.

When surrogate consent is used, the investigator must document in writing the name of the surrogate and that he/she: 1) is aware of his/her responsibility, 2) has been informed about risks/benefits of the study, 3) is aware that the subject had consented to participate, if applicable, 4) is aware of his/her rights to withdraw his/her consent, 5) may contact the PI or Research Service for questions/problems, 6) is aware that the subject, if possible, has given his/her assent to participate in the study, 7) will be informed of future information that is needed to be an informed participant. Progress notes during the period of surrogate consent should note that subject him/herself demonstrates no dissent from participation in the study.

NOTE: Per guidance from the privacy office, *only* court-appointed surrogates can sign HIPAA Authorization. Thus, in cases where the research targets those with decision-making incapacity, or, may incidentally enroll subjects with decision making incapacity, a HIPAA Authorization must be separated from the consent form, if other than court-appointed surrogates are signing consent.

When Subjects are physically or mentally unable to sign HIPAA authorization (VA Form 10-0493), the VA IRB has established the following process:

- TWO adults who are NOT part of the Research Team shall witness the subject's agreement to provide authorization. This can be accomplished by signing *and* dating the HIPAA Authorization in the open area on the signature page indicating "witness." Witness signature must NOT be on the Subject signature line. That will remain blank.
- The PI will document this circumstance in the Research Note in the Health Record. If there is no Health Record the PI is to document the circumstance in the investigator's research file.

NOTE: In the event the target population is physically unable to sign the HIPAA Authorization the IRB will consider alteration of Authorization to Use or Disclose Protected Health Information in Research

## 6.10 Research Involving Other Potentially Vulnerable Adult Subjects.

1. **Research Involving Employees, Students, and Trainees**. Employees, students, and trainees at the VANEOHS should also be considered vulnerable subjects. Thus, the IRB should uphold the same standards in approving research involving these groups as other vulnerable subjects.

2. **Research Involving Deceased Persons**. Research involving deceased persons is not covered by the VA or FDA human subject regulations or the Common Rule. However, such research may be covered under applicable state law.

# Chapter 7 Reporting of Unanticipated Problems Involving Risks to Participants or Others

## 7.1 Purpose

VANEOHS complies with VA and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials and relevant federal agencies and departments.

The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the auspices of VANEOHS.

## 7.2 Definitions

**Unanticipated problems involving risk to participants or others.** Unanticipated problems involving risks to participants or others refer to any problem, event, or new information that:

1. Is unexpected (in terms of nature, severity, or frequency) given
    a. the research procedures that are described in the protocol-related documents, such as the IRB-approved Research Plan and informed consent documents; and
    b. the characteristics of the subject population being studied;
2. Is related or possibly related to participation in the research, and
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

**Adverse Event.** An adverse event (AE) is defined as any untoward occurrence (physical, psychological, social or economic) in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article. Some adverse events are expected and can be anticipated.

**Serious Adverse Event**. A serious adverse event (SAE) is defined as death; a life threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

**Unexpected Adverse Event.** An unexpected adverse event (UAE) is any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

**Adverse Device Effect.** An adverse device effect (ADE) is any adverse event/effect caused by or associated with the use of a device that is unanticipated and has not been included in the protocol or the Investigator's Brochure.

**Related.** There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

**Substantive Action.** An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

**Unexpected Death.** The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not associated with the research is also not an "unexpected death" for purposes of the reporting requirements of these procedures.

## 7.3 Data Safety Monitoring Plan

Where appropriate, a research plan should make adequate provisions for monitoring data collected to provide for the safety of participants. The initial research plan submitted to the IRB should describe the procedures for data safety monitoring and reporting of adverse events and unanticipated problems involving risks to subjects or others. Provisions for a DSMB or any independent safety monitoring board and the procedures planned for transmitting the results to the IRB is reviewed at initial review. Otherwise an explanation as to why it is not necessary must be approved by the IRB.

## 7.4 Procedures

### 7.4.1 Reporting

Investigators must report all problems listed below to the IRB within five (5) days of receiving notice of the event, if the event requires immediate intervention to prevent serious harm to participants or others.

Investigators must report all other problems listed below occurring at the local VA research site and non-local VA research sites to the IRB as soon as possible but no later than five (5) business days from the date of the event or from the date the investigator is notified of the event.

Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

#### 7.4.1.1 Reportable Events

Investigators must promptly report within five (5) business days the following to the IRB if the events, problems, or new information occur within thirty (30) days of a participants' active participation or treatment in a research study: (See VHA Handbook 1058.01)

1. Unanticipated problems involving risks to subjects or others
2. Serious unanticipated problems involving risks to subjects or others, these include:
   a. Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.
   b. Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individual(s), or leads to serious complications or death.
   c. Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the facility's research projects.
   d. Any DMC, DSMB, or DSMC report describing a safety problem.
   e. Any sponsor analysis describing a safety problem for which action at the facility level may be warranted.
   f. Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others;
   g. Any problem reflecting a deficiency that substantively compromises the effectiveness of a facility's human research protection or human research oversight programs.

3. Any local SAE that is both unanticipated and related to the research must be reported in writing, within five (5) business days of becoming aware of the event.

4. Investigators must report the following events immediately to the VANEOHS Privacy Officer or VANEOHS ISSO, as appropriate, upon discovery of the event(s):

   a. Unauthorized use, loss, or disclosure of individually identifiable patient information.
   b. Violations of information security requirements.

**7.4.2 Submission of Reports**

Investigators and/or study staff must report any event, problem, or new information that may represent unanticipated problems involving risks to participants and others to the IRB Office in writing using the Unanticipated Event Reporting Form. The written report should contain the following:

1. Detailed information about the possible unanticipated problems, including relevant dates.
2. Any corrective action, planned or already taken, to ensure that the possible unanticipated problems are corrected and will not occur again.

3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, psychological, or economic harm and any plan to address these consequences.
4. A copy of the latest IRB approved stamped consent form(s) and latest IRB approved stamped research plan as appropriate
5. Any other relevant information.
6. Any other information requested by the IRB Office.

### 7.4.3 IRB Procedures for Handling Reports of Possible Unanticipated Problems

A report of a possible unanticipated problem involving risks to participants or others will be forwarded by the IRB Administrative Staff to the IRB Co-Chairperson and/or other experienced member(s) designated by the IRB Co- Chairperson. If the IRB Administrative Staff believe that immediate intervention may be required to protect participants or others from serious harm, the report will be immediately forwarded to the IRB Co-Chairperson.

Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the IRB Administrative staff will notify the PI on the study when appropriate.

The IRB Co-Chairperson (or designee) will review the report to determine if the reported event represents an unanticipated problem involving risk to participants or others.

The IRB Co-Chairperson (or designee) will review each event to determine:
1. Whether the event is unforeseen
2. Whether the event indicates that subjects or others are at increased risk of harm If the IRB Co-Chairperson (or designee) determines that the event is unforeseen **and** indicates that subjects are at increased risk of harm (both 1&2 above), the event is considered an unanticipated problem involving risks to subjects or others. Otherwise the problem is considered NOT to represent an unanticipated problem involving risks to subjects or others.

**Unanticipated Problem Involving Risks to Subjects or Others**. If the IRB Co-Chair or designee has determined the event to be an unanticipated problem involving risks to subjects and/or others it will be referred to the convened IRB for review. Additionally, it will be reported to the medical center Director within five (5) working days.

Event Not an Unanticipated Problem Involving Risks to Subjects or Others. If the event is determined NOT to be an unanticipated problem involving risks to subjects or others, the following actions may be taken:
1. If the event is a result of research noncompliance, the event will be reviewed.
2. At the discretion of the IRB Co-Chairperson (or designee) the event is referred to the convened IRB for review and further action.
3. No further action taken. Filed in the IRB study file without further review by the convened IRB.

**7.4.4 IRB Review**

1. The primary reviewer(s) (those reviewers selected at initial study review) will be given the "Unanticipated Event Reporting Form," Research Plan, informed consent form(s), and other documents as applicable:

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2. The members of the convened IRB will be given the event report and accompanying documents, which may include recommendations from the IRB Co-Chairperson or designee. The primary reviewer(s) will provide a summary of the event to the convened IRB. After review of the protocol and event report, the full IRB will make findings and recommendations based on the following considerations:

a. Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.

b. What action in response to the report is appropriate.

c. Whether suspension or termination of approval is warranted.

d. Whether further reporting to Institutional and/or federal officials is required.

3. If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

a. No action

b. Requiring modifications to the protocol

c. Revising the frequency for continuing review

d. Modifying the consent process

e. Modifying the consent document

f. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)

g. Providing additional information to past participants

h. Requiring additional training of the investigator and/or study staff

i. Other actions appropriate for the local context

4. If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

a. Requiring modifications to the protocol

b. Revising the continuing review timetable

c. Modifying the consent process

d. Modifying the consent document

e. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation)

f. Providing additional information to past participants

g. Requiring additional training of the investigator and/or study staff

h. Reconsidering approval

i. Requiring that current participants re-consent to participation

j. Monitoring of the research

k. Monitoring of the consent

l. Referring the problem to other organizational entities (e.g., legal counsel, risk management, institutional official)

m. Suspending the research
n. Terminating the research
o. Other actions appropriate for the local context

5. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the R&D Committee, medical center Director, ORO, OHRP, and FDA (if FDA-regulated research) through the medical center Director.
6. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will forward its findings and recommendations, including the minutes of the IRB meeting, to the R&D Committee. The IRB will also:

a. Notify the investigator in writing of its findings, with copies to the Service Chief of the investigator's department and/or research unit, and the investigator's supervisor, and

b. Report its findings and recommendations to the medical center Director for further reporting to the appropriate federal officials (ORO, OHRP, and FDA) and

c. Follow reporting requirements detailed in medical center policy 151-019 Research Compliance.

## 7.5 Non-Reportable Events

All events, problems, and new information that do not meet the above reporting requirements must be reported to the IRB in summary form at the time of the next continuing review.

The IRB recognizes that sponsors may require that the PI report all serious adverse events and IND safety reports to the IRB. The IRB complies with this request in an efficient manner to acknowledge receipt of these reports.

PIs should report adverse events and IND safety reports that do not meet the above reporting requirements by using the Tracking Log for Non-Reportable Events form.

Upon receipt, the IRB Administrative Staff will review the Tracking Log for Non-Reportable Events and check the form for completeness. The form will be returned to the investigator if the form is incomplete.

If the investigator answered yes to all three of the questions listed below for a specific event, the IRB staff will contact the investigator to request that the investigator complete an Unanticipated Event Reporting form.

1. Did the event, problem, or new information harm one or more participants or others, or place one or more participants or others at increased risk of harm?

2. Was the event, problem, or new information unexpected (in terms of nature, severity, or frequency) given the procedures described in the protocol related documents and the characteristics of the population being studied?

3. Was it more likely than not that the event was caused by the research procedures or affects the rights and welfare of current participants?

Otherwise, the IRB Administrative Staff will sign and date the form, and return a copy of the form to the PI.

## Chapter 8 Conflict of Interest in Research

## 8.1 Purpose

The following procedures are intended to preserve public trust in the integrity and quality of research at the VANEOHS by minimizing actual or perceived conflict of interest in the conduct of research.

## 8.2 Definitions

**Conflict of Interest.** A COI occurs when any financial arrangement, situation, or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. It includes any situation in which financial or personal obligations may compromise, or present the appearance of compromising, an individual's or group's professional judgment in conducting or reporting research.

**Financial Interest:** Financial interest means anything of monetary value or anything of monetary value in components whose interests could reasonably affect, or be affected by, the research. Financial interest includes, but is not limited to, the following:

1. Any financial arrangement whereby compensation to the investigator could influence, or be influenced by, the outcome of the study;
2. Salary and other payments for services (e.g., consulting fees, honoraria, etc.);
3. Payments of other sorts from the sponsor of the research (e.g., a grant to fund other ongoing or additional research, compensation in the form of equipment, retainer for on-going consultation, etc.);
4. Equity interests (e.g., stocks, stock options, or other ownership interests);
5. Proprietary interests or intellectual property rights (e.g., patents, trademarks, copyrights, licensing agreements, royalties, etc.); and
6. Non-cash items such as travel expenses or business gifts.

**Non-financial Conflict of Interest.** Non-financial conflict of interest may exist when an individual serves dual roles, such as health care provider and investigator. Other interests such as publication, promotion or tenure, can also become conflicts of interest that may affect an individual's judgment. Membership in oversight committees such as the R&D Committee and IRB as well as positions of authority may pose potential conflicts of interest. Any position that includes responsibilities for the review and approval of research projects or contracts other than his/her own may potentially affect the design of, decisions made, and/or action taken surrounding a specific study.

**Compensation.** Compensation resulting from a favorable outcome of clinical studies in the form of equity interest in the sponsor of a covered study or in the form of compensation tied to sales of a product, such as royalty interest.

**Significant equity interest.** Significant equity interest in the sponsor of a covered study means any ownership interest, stock options, or other financial interest in a non-publicly

traded corporation, or any equity interest in a publicly traded corporation that exceeds $10,000 during the time the clinical investigator is carrying out the study and for one year following completion of the study.

**Proprietary interest.** Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright, or licensing agreement.

**Covered clinical study.** Covered clinical study is any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase I tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols. An applicant may consult with FDA as to which clinical studies constitute “covered clinical studies” for purposes of complying with financial disclosure requirements.

**Significant payments.** Significant payments of other sorts means payments, that have a monetary value of more than $10,000, exclusive of the costs of conducting the clinical study or other clinical studies, made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the investigator is carrying out the study and for one year following the completion of the study.

**Applicant.** Applicant means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

**Sponsor.** Sponsor of the covered clinical study means the party supporting a particular study at the time it was carried out.

**Immediate Family Member(s).** Immediate family member(s): having a relationship to a person (whether by blood, law, or marriage) as a spouse, parent, child, grandparent, grandchild, stepchild, or sibling.

**Disclosure.** Disclosure is the formal written process of documenting all aspects relating to the development of potential intellectual property for the purpose of determining and assigning ownership.

**Equity.** The money value of a property or of an interest in a property in excess of claims or liens against it.

**Institutional conflict of interest.** An institutional conflict of interest may occur when the institution, or any of its senior management, or an affiliate foundation or organization has an external relationship or financial interest in a company or organization that itself has a financial interest in a VA investigator’s research project.

**Institutional officials.** These are individuals in a position to make decisions with institution-wide implications. These include the medical center Director/Institutional Official (IO), COS, ACOS/R&D, and other senior officers and management officials.

**Intellectual Property (Invention).** Intellectual property is any art, machine, manufacture, design, or composition of matter, or any variety of plant, which is or may be patentable under the patent laws of the United States.

**Inventor.** The inventor is the individual responsible for the conception or reduction to practice of a device or process.

**Patent.** A patent is an official written document securing to an inventor for a term of years the exclusive right to make, use, or sell an invention.

**Re-disclosure.** Re-disclosure is the formal written process of documenting all aspects relating to any improvement of a previously disclosed invention for the purpose of issuing a new determination on the improved invention.

**Royalty.** A royalty is compensation for an invention.

## 8.3 Individual Conflicts of Interest

These procedures apply to both financial and non-financial conflicts of interest and are guided by Code of Federal Regulations (Title 42 of the Code of Federal Regulations (CFR) Part 50 Subpart F) that promotes objectivity in research to ensure COIs do not adversely affect the protection of participants or the credibility of the VANEOHS HRPP.

All investigators must comply with applicable VHA policies, federal and state regulations regarding conflicts of interest in research.

For clinical studies involving the use of new human drugs and biological products or medical devices, certifications and disclosure requirements are defined in FDA regulations, Title 21 CFR Part 54.

All VA employees must comply with the criminal statute pertaining to acts affecting personal or imputed financial interest (18 U.S.C. Section 208) and the Standards of Ethical Conduct for Employees of the Executive Branch (5 CFR Part 2635).

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and can only strengthen the research process. Therefore, conflicts of interest must be eliminated when possible and effectively disclosed and managed when they cannot be eliminated.

### 8.3.1 Responsibilities Institutional Official (IO)

The medical center Director is the IO who has an obligation to preserve the public trust in the integrity and quality of research and to exercise prudent stewardship of public resources, including public funds that support research programs. The IO is responsible for the R&D program within the medical center and as such, represents the facility in issues related to COI in research and administers the medical center's program related to financial COI in research. The IO appoints the COI Administrator and the COI Committee

to oversee the program.

**Conflict of Interest Administrator**

The COI Administrator is responsible for conducting the review process, including initial review of the disclosure forms prior to the R&D Committee review and determines whether a referral to General Counsel is deemed as necessary. He/she serves as staff for the review process; and maintains records and official files for the COI process. The ACOS/R&D and/or AO/R&D may serve as the COI Administrator. The ACOS/R&D and AO/R&D are members of the Case Outside Interest Committee representing the VANEOHS.

**General Counsel**

General Counsel is responsible for assisting the COI Administrator in working with study staff and/or members of the R&D Committee, IRB and/or IACUC and the ACOS/R&D to manage any potential COI risks.

**R&D Committee**

The R&D Committee is responsible for reviewing and monitoring possible financial COI, as well as carrying out the recommendations from the COI Administrator or General Counsel.

**Institutional Review Board (IRB)**

The IRB is responsible for reviewing and requiring appropriate changes in protocols and informed consent forms affected by COI for research involving human subjects.

**PIs and Study Staff**

The PI is responsible for ensuring that any potential financial COI, either for him/herself, or study staff with responsibility for designing, conducting or reporting the research, as well as for spouses and dependent children, is disclosed in the research project application process and that any subsequent financial COI arising after the initial application is also reported.

## 8.3.2 Procedures

### 8.3.2.1 Investigator/Staff Disclosure of COI:

Investigators and study staff are required, to disclose potential COIs that may appear to bias any research under their influence through the following procedures:

Disclosures are made by completing the Conflict of Interest Assessment Form at the time of initial review of a protocol. This applies to all proposals submitted to VANEOHS for local review, and to proposals submitted to VACO and other agencies for funding consideration.

Disclosures are also completed at the time of continuing review, and whenever any changes have occurred to the previously submitted disclosure.
The COI Administrator reviews the COI disclosures submitted at the time of the initial submission. The IRB Administrative Staff review the COI disclosures submitted at continuing review or if a there is a change in COI disclosure. If an investigator or study

staff responds affirmatively to the existence of a potential conflict, the IRB Administrative Staff notify the COI Administrator.

#### 8.3.2.2 IRB Member Disclosure of COI

See Section 3.9 IRB Member Conflict of Interest.

#### 8.3.2.3 COI Administrator Evaluation of COI for PIs and Study Staff

1. If the PI or any study staff responds affirmatively to the existence of a potential conflict, the COI Administrator will request additional information from the PI or study staff, as necessary. He/she will review the materials and determine whether the proposed project could reasonably appear to be directly and significantly affected by the related potential financial COI of the PI or study staff. A direct impact could occur when:
    a. The project results would be directly relevant to the development, manufacture or improvement of the products or services of an organization in which the PI or study staff has a financial COI;
    b. The organization in which the PI or study staff has a financial COI is a proposed subcontractor in the project;
    c. There is a relationship between the project sponsor and the PI or study staff outside the project that has the potential to affect performance in the project.
2. If the COI Administrator determines there is no reasonable basis to conclude that the design, conduct or reporting of the project could be directly and significantly affected by the potential financial COI, he/she will inform the PI (and member of the study staff, when applicable), the R&D Chairperson and IRB Co-Chairperson in writing that the project has been cleared of COI. A copy of the notification will be reviewed by the IRB and placed in the study file.
3. If the COIA determines that the design, conduct or reporting of the project could be directly and significantly affected by the potential financial COI reported by the PI or study staff, then he/she will contact General Counsel.
4. General Counsel will make a decision as to whether the project should proceed and under what conditions or restrictions that might occur. These recommendations will be made in writing to the PI (and member of the study staff, when applicable), R&D Chairperson and IRB Co-Chairperson. This information will be strictly confidential and will be kept in a secure file maintained by the COI Administrator.
5. If during the conduct of a project any new or related potential financial COI described above should arise, the PI must disclose this to the R&D, IRB and/or IACUC through the COIA. A review will be conducted as with the original disclosure.
6. Disclosure must be made at least annually. For human subject research and animal studies, this will be done in conjunction with the application for continuing review.

### 8.3.2.4 IRB Evaluation of COI

The IRB will review the COI Administrator and/or General Counsel's determinations and make recommendations of all potential conflicts of interest. The IRB will determine the following:

- Whether the conflict, financial or non-financial, affects the protections of research participants,
- Whether a conflicting interest might adversely affect the credibility of the HRPP thus creating the appearance of conflicts of interest.

### 8.3.2.5 R&D Committee Evaluation of COI

The R&D Committee will review the actions taken by the IRB. The committee will determine what actions in addition to those required by the IRB should be taken by the institution or the investigator to manage, reduce or eliminate the COI.

Points to consider are:

- How is the research supported or financed,
- Who designed the study,
- Will the institution receive any compensation,
- Is the institution an appropriate site for the research.

### 8.3.2.6 Management of COI:

The IRB will determine if the rights and welfare of human research participants will be better protected by any or a combination of the following:

1. The PI or the study staff will sever relationships creating the conflict.
2. The PI or the study staff will divest significant financial interests.
3. The PI will disclose the relationship with the sponsor on all publications, in the consent form provided to human subjects, and in other appropriate public forum (including manuscripts, abstracts and lectures).
4. The PI will separate the research from consulting, providing an acceptable detailed written plan for achieving this.
5. The PI will substitute someone else to serve as project PI and is appropriately distanced from the conduct of the research.
6. The PI will secure an independent reviewer for monitoring of the research and analysis of the data.
7. The PI will modify the protocol or safety monitoring plan.
8. The PI will be disqualified from participating in all or a portion of the research

#### 8.3.2.7 Failure to Comply with the COI Policy

Failure to comply with conflict of interest policies and procedures and/or committee determinations constitutes research noncompliance and will be investigated according to medical center policy 151-019 Research Compliance Reporting Requirements.

## 8.4 Institutional Conflict Of Interest

See Medical Center Policy 151-020 Institutional Conflict of Interest in Research.

## Chapter 9 FDA-Regulated Research

## 9.1 Purpose

FDA regulations apply to any research that involves a *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56, as well as, where appropriate, 45 CFR 46.

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA and VA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA and VA regulations.

The following procedures describe the review of FDA-regulated research conducted under the auspices of VANEOHS.

## 9.2 Definitions

**Investigational Drug.** An investigational drug is a drug or biological agent that is used in a clinical investigation for which the PI or a sponsor has filed an Investigational New Drug (IND) application (21 CFR Part 312). The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug (21 CFR 312.3). However, according to VHA Handbook 1200.05 an investigational drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

**Emergency Use.** Emergency use is defined as the use of an investigational drug or biological product in a human subject who is in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

**Investigational Device.** An investigational device is a medical device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. As further stated, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.

**IDE.** IDE means an investigational device exemption in accordance with 21 CFR 812.

**Significant Risk (SR) Device.** Significant risk device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating

disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

**Non-Significant Risk (NSR) Device.** A non-significant risk device is an investigational device other than a significant risk device.

**Humanitarian Use Device (HUD)**. Humanitarian Use Device is a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 4,000 individuals in the United States per year. A humanitarian device exemption application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. The labeling for an HUD must state that the device is a HUD and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

**Unexpected Adverse Device Effect.** An unexpected adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

## 9.3 Procedures (Best Practice)

At initial submission, the PI must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The PI may use the FDA Determination Checklist to assist in making this determination.

During the pre-review process, the IRB Administrative Staff will confirm whether FDA regulations are applicable using the FDA Determination Checklist. Investigational Drugs and Devices in Research.

### 9.3.1 IND/IDE Requirements

The PI must indicate on the IRB application whether the research involves investigational drugs or devices. If so, the PI must indicate if there is an IND/IDE for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations. Documentation of the IND/IDE could be a:

1. Industry sponsored protocol with IND/IDE.
2. Letter from FDA.

3. Letter from industry sponsor.
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, NSR device studies follow abbreviated IDE requirements and do not have to have an IDE application approved by the FDA. If a sponsor has identified a study as NSR, then the investigator must provide an explanation of the determination. If the FDA has determined that the study is NSR, documentation of that determination must be provided.

If the research involves drugs or devices and there is no IND/IDE, the PI must provide a rationale why it is not required.

The IRB will review the application and determine:

9. Whether there is an IND/IDE and if so, whether there is appropriate supporting documentation.
10. If the research involves drugs or devices with no IND/IDE, and whether the research meets the criteria below.

### 9.3.2 IND Exemption

For drugs, an IND is not necessary if all seven of the following conditions are met:

1. The drug being used in the research is lawfully marketed in the United States;
2. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
3. The research is not intended to support a significant change in the advertising for the product;
4. The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
5. The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively);
6. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7);
7. The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research).

Note: The following are also exempt from the IND requirements: (a) a clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND; and (b) a drug intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.160 .

For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

1. It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
2. It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
3. It is shipped in compliance with 21 CFR 312.160

### 9.3.3 Exempted IDE Investigations

For devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence;
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

## 9.4 Responsibilities

### 9.4.1 PI

1. The PI is responsible for ensuring that the research is conducted according to all regulatory guidelines and VANEOHS policies and procedures
2. The PI must obtain approval from the R&D Committee and IRB before initiating any research activities.
3. The PI proposing the drug/device research will be required to provide a plan – to be evaluated by the R&D Committee and the IRB - that includes storage, security, and dispensing of the drug/biologics/device.
4. The PI is responsible for the investigational drug/device accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. The PI will delegate the responsibility for drugs/biologics accountability to the Pharmacy Service (See medical center policy 119-019 “Investigational Drugs for Patient Use.”).
5. All investigational drugs will be stored under lock and key and dispensed by the Pharmacy Service.
6. All devices received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI’s control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation (See medical center policy 151-015 Investigational Devices Used in Human Subjects” for an “Example of Investigational Device Control Log.”).
7. The PI shall report all unanticipated problems involving risk to subjects or others to the IRB according to the procedures outlined in Section 7.
8. For research involving investigational new drugs:
    a. The PI must obtain approval from the P&T Committee.
    b. The PI must provide all required documents to the Research Pharmacist. Both for initial approvals and Continuing reviews, changes in protocols affecting the research pharmacy 10-9012 changes etc. The PI must send a signed copy of the approved VA Informed Consent Form to the Pharmacy Service to document each subject’s consent to participate in the study.
    c. The PI must send copies of continuing review approval documents.
    d. The PI must inform the R&D Committee, IRB, and Pharmacy Service when a study involving investigational drugs has been terminated by the sponsor.
    e. The PI will report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.
    f. The PI will maintain the following:
        i. Current curriculum vitae (CV)

ii. Protocol

iii. Records of receipt and disposition of drugs

iv. List of any co-investigators with their curriculum vitae

v. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation, and

vi. Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to Pharmacy Service and the IRB in the manner defined by the protocol.

vii. R&D, IRB and P&T Committee letters of approval.

viii. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.

9. For research involving investigational devices:

a. The PI must obtain approval from the Environment of Care (EoC) Committee for any electrically line-operated devices, that will come in contact with human subjects and that are not used for their standard application or if the device is specially constructed by research staff.

b. If a device is considered NSR by the PI or sponsor, but after review the IRB determines the device to have significant risk, upon receipt of written notice the PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.

c. If the PI is storing the devices, he/she must maintain a log indicating the identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining. The PI will document in a CPRS progress note that he/she provided education on its use to the subject.

d. The PI will maintain the following:

i. Current curriculum vitae (CV),
ii. Protocol of the study,
iii. Records of animal study reports,
iv. Records of receipt and disposition of devices,
v. List of any co-investigators with their curriculum vitae,
vi. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation,
vii. Case histories with particular documentation on evidence of effects. Emphasis is on safety and possible untoward happenings. All adverse

device effects are reportable.

viii. R&D, IRB letters of approval and the EOC Committee approval letter if applicable.

ix. Device training.

x. Other documents as outlined in the Human Subject Protection Program Standard Operating Procedures.

e. Following completion of the study the termination procedure for investigational drugs must be applied if pharmacy control, or if the devices are kept by the investigator the log must be completed regarding the receipt, use and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

f. If, after use, the PI keeps the devices, he/she must maintain a log regarding the receipt, use and/or re-dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

g. The PI will submit to the sponsor and to the IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

10. When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all of the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The Research Plan asks the PI if he/she also acts as the sponsor of the research and, if so, asks him/her to affirm that he/she has reviewed the Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor and will comply with the regulatory responsibilities of a sponsor. The Research Service will conduct education programs for investigators holding an IND or IDE on the sponsor regulations and periodically conduct random audits of PIs holding an IND or IDE as per the Research Quality Improvement Program.

### 9.4.2 IRB

1. The IRB will review the research in accordance with the following requirements and the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

2. For research involving investigational devices:
   a. Unless the FDA has already made a risk determination for the study, the IRB will review NSR studies and determine if the device represents significant or non-significant risk and report the findings to the PI in writing. The IRB will consider the risks and benefits of the medical device compared to the risks and benefits of alternative devices or procedures. Non-significant risk device studies do not require submission of an IDE application but must be conducted in accordance with the abbreviated requirements of IDE regulations. If the study that has been submitted as NSR is considered SR, the IRB may approve the study, but the study cannot begin until an IDE is

obtained.

b. The IRB will not review protocols involving significant risk devices under expedited review.

c. The IRB will document in the minutes and provide written documentation to the PI of the rationale for determining whether a device is classified as NSR/SR.

d. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final and the IRB does not need to make a risk determination.

### 9.4.3 R&D Committee Coordinator

The R&D Committee Coordinator will forward the R&D Committee and IRB approval letters, the signed VA Form 10-9012, Investigational Drug Information Record and the approved protocol to the Pharmacy Service.

## 9.5 Emergency Use

### 9.5.1 Emergency Exemption from Prospective IRB Approval.

FDA defines emergency use as the use of an investigational drug, device, or biological product in a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. If all conditions described in 21 CFR 56.102(d) exist, then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Informed consent is required unless the conditions for exemption are met (see below Section 9.6.2). The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review.

The clinician is strongly encouraged to notify the COS or designee in the event that he/she plans to use the emergency exemption from prospective IRB approval. This administrative notification is not required in the event that time does not permit.

The clinician is required to notify the pharmacy of the emergency use of an investigational drug or biologic.

If the clinician notified the IRB prior to the emergency use of an investigational test article, the circumstances will be reviewed expediently by the IRB Co-Chairperson and the COS to determine that it meets FDA regulations and the clinician will be advised accordingly.

All after-the-fact reports to the IRB of emergency use will be reviewed by the IRB Co-Chair to determine the circumstances for compliance with FDA regulations.

### 9.5.2 Emergency Waiver of Informed Consent

An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the PI and an independent physician, who is not otherwise participating in the clinical investigation,

certify in writing all four of the following specific conditions exist:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article;
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
3. Time is not sufficient to obtain consent form the subject's legally authorized representative;
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the PI must be reviewed and evaluated in writing by an independent physician within 5 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB.

#### 9.5.2.1 Expanded Access of Investigational Drugs

FDA regulations allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs, agents, or biologics through the following methods:

1. Compassionate Use: The term "compassionate use" is erroneously used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or HHS regulations. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.
2. Group C Treatment Investigational New Drug (IND): A means for the distribution of investigational drugs, agents, or biologics to oncologists for the treatment of cancer under protocols outside controlled clinical trials. Group C drugs, agents, or biologics usually have shown evidence of relative and reproducible efficacy in a specific tumor type. Although the FDA typically grants a waiver for most drugs used in Group C Treatment IND protocols, VANEOHS IRB requires prospective IRB review and approval.
3. Open – Label Protocol: A study designed to obtain additional safety data, typically done when the controlled trial has ended and treatment continues. The purpose of such a study is to allow subjects to continue to receive the benefits of the investigational drug, agent, or biologic until marketing approval is obtained. Prospective IRB review and approval is required.
4. Parallel Track: A method approved by the FDA that expands the availability of investigational drugs, agents, or biologics as quickly as possible to persons with AIDS and other HIV-related diseases. These drugs, agents or biologics are utilized in separate protocols that "parallel" the controlled clinical trials and are essential to

establish the safety and effectiveness of these new drugs, agents, or biologics. Although the Secretary of the Department of Health and Human Services may, on a protocol-by-protocol basis, waive the provisions of 45 CFR Part 46 where adequate protections are provided through other mechanisms, prospective IRB review and approval is required by the VANEOHS IRB.

5. Treatment IND or Biologics: A mechanism for providing eligible subjects with investigational drugs (as early in the drug development process as possible) for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The FDA defines an immediately life-threatening disease as a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. The FDA will permit an investigational drug to be used under a treatment IND after sufficient data have been collected to show that the drug “may be effective” and does not have unreasonable risks. Prospective IRB review and approval is required.

    a. There are four requirements that must be met before a treatment IND can be issued:

        i. The drug is intended to treat a serious or immediately life-threatening disease;

        ii. There is no satisfactory alternative treatment available;

        iii. The drug is already under investigation or trials have been completed; and

        iv. The trial sponsor is actively pursuing marketing approval.

    b. The FDA identifies two special considerations when a patient is to be treated under a Treatment IND:

        i. Informed Consent. Informed consent is especially important in treatment use situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications which have not been proven either safe or effective in a clinical setting. Both the setting and their desperation may work against their ability to make an informed assessment of the risk involved. Therefore, theIRB should ensure that potential subjects are fully aware of the risks involved in participation.

        ii. Charging for Treatment INDs. The FDA permits charging for the drug, agent, or biologic when used in a Treatment IND. Therefore, the IRB Committee should pay particular attention to Treatment INDs in which the subjects will be charged for the cost of the drugs. If subjects will be charged for use of the test article, economically disadvantaged persons will likely be excluded from participation. Charging for participation may preclude economically disadvantaged persons as a class from receiving access to test articles. The IRB should balance this

interest against the possibility that unless the sponsor can charge for the drug, it will not be available for treatment use until it receives full FDA approval.

6. Single-Patient Use: The use of an investigational drug outside of a controlled clinical trial for a patient, usually in a desperate situation, who is unresponsive to other therapies or in a situation where no approved or generally recognized treatment is available. There is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through the sponsor under a treatment protocol, or through the FDA, by first obtaining the drug from the sponsor and then submitting a treatment IND to the FDA requesting authorization to use the investigational drug for treatment use. Prospective IRB review and approval is required (See 5 above).
7. Emergency IND: The emergency use of an unapproved investigational drug, agent, or biologic requires an emergency IND. The FDA has established mechanisms and guidance for obtaining an Emergency IND for the use of investigational drugs, agents, or biologics.

#### 9.5.2.2 Emergency Waiver of IND

FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

#### 9.5.2.3 Expanded Access of Investigational Devices

1. Compassionate Use (or Single Patient/Small Group Access). The compassionate use provision allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group. It must be a serious disease or condition and no alternative treatment available. Prior FDA approval is needed before compassionate use occurs.
2. Treatment Use. An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. The criteria include:

a. Life-threatening or serious disease
b. No alternative
c. Controlled clinical trial
d. Sponsor pursuing marketing approval

3. Continued Access. FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational medical device while the marketing application is being prepared by the sponsor or reviewed by FDA. There must a public health need or preliminary evidence that the device will be effective and there are no significant safety concerns.

## 9.6 Humanitarian Use Devices (HUD)

In accordance with 21 CFR 814.124, treatment with a HUD is subject to full board initial and continuing review by the R&D Committee and IRB. At the time of review, the IRB will determine if written consent from participants for use of the HUD is necessary. If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior IRB approval. In this instance, approval must be obtained from the COS, and the PI is required to provide written notification of the use to the IRB within five days after use of the device. The IRB requires that written notification include identification (specification without identifiers) of the patient, the date on which the device was used, and the reason for the use.

It is the responsibility of the PI to notify the FDA within five days if the IRB withdraws approval for use of a HUD. The PIs are reminded that HUDs are for clinical use only and HUDs can be used only for purposes outlined in the approved IRB application.

## 9.7 Gene Transfer Research

Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the NIH Office of Biotechnology Activities.

FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.

DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) (VANEOHS has an MOU with Case to utilize their IBC) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).

While the RAC is advisory to the Director of the NIH, compliance with its guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

## 9.8 Planned Emergency Research

An exception under FDA regulations at 21 CFR 50.24 permits planned research in an emergency setting without the informed consent of the subjects. Please note that planned emergency research is not permitted in the VA.

## Chapter 10 Investigator Responsibilities

## 10.1 Purpose

Principal Investigators (PI) are ultimately responsible for the conduct of research. Principal Investigators must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the local SOPs regarding the conduct of research and the protection of human subjects. Principal Investigators may delegate research responsibility. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

As per VHA Handbook 1200.05 the IRB recognizes one PI for each project. The PI must have a VA paid appointment and cannot be a student or trainee.

## 10.2 PI Responsibilities

In order to satisfy the requirements of this policy, PIs who conduct research involving human subjects must:

1. Develop and/or conduct research that is in accordance with the ethical principles outlined in the Belmont Report.
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects. In the event that the PI did not design the research study, the PI determines that design is sound to carry out the research. Ensuring the research protocol contains all required information.
3. Obtain all written approvals before initiating research. This includes but is not limited to IRB, R&DC and SRS approval.
4. Implementing the research study as approved by the IRB and in accordance with other required approvals.
5. Have sufficient resources necessary to protect human subjects, including:
    a. Access to a population that would allow recruitment of the required number of subjects.
    b. Sufficient time to conduct and complete the research.
    c. Adequate numbers of qualified staff.
    d. Adequate facilities.
    e. A process to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.
    f. Availability of medical or psychological resources that subjects might require as a consequence of the research.
6. Assure that all key personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are

based;

7. Protect the rights and welfare of prospective subjects.
8. Ensure that risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes
9. Recruit research subjects in a manner that is fair, ethical and equitable.
10. Obtain and document informed consent as required by the IRB and ensuring that no human subject is involved in the research prior to obtaining their consent; If the PI does not personally obtain informed consent, the investigator must formally and prospectively designate to another research team member in writing in the approved protocol the responsibility for obtaining informed consent.
11. Have plans to monitor the data collected for the safety of research subjects.
12. Protect the privacy of subjects and maintain the confidentiality of data;
13. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, include additional safeguards in the study to protect the rights and welfare of these subjects;
14. Have a procedure to receive complaints, concerns, or requests for additional information from subjects and respond appropriately.
15. Ensure that pertinent laws, regulations, and institution procedures and guidelines are observed by participating investigators and study staff.
16. Comply with all IRB decisions, conditions, and requirements.
17. Ensure that protocols receive timely continuing review and approval from the R&D Committee and IRB.
18. Promptly report to the IRB any unanticipated problems involving risks to subjects or others.
19. Disclose conflicts of interest to the IRB.
20. Obtain IRB review and approval in writing before instituting changes made to approved protocols or consent forms.
21. Promptly report any changes in the PI to the IRB.
22. Seek IRB assistance when in doubt about whether proposed research requires IRB review.
23. Maintaining Investigator’s Research Records to include the following when relevant to the study
    a. Copies of all IRB-approved versions of the protocol and amendments
    b. Case report forms and supporting data, including, but not limited to, signed

and dated informed consent forms and HIPAA authorizations

c. Documentation on each subject including, but not limited to:

i. Informed consent

ii. Interactions with subjects by telephone or in person

iii. Observations

iv. Interventions

v. Other data relevant to the research study, including, but not limited to: progress notes; research study forms; surveys and questionnaires; reports of adverse events; data analyses; reports including, but not limited to, abstracts and other publications; all correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO; and a master list of all subjects for whom informed consent has been obtained in the study

d. Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements, and

e. Accounting of Disclosure must be maintained for each disclosure of information from the study to a non-VA entity (The facility Privacy Officer can assist in providing a mechanism to account for this disclosure)

f. Maintain a Master List of All Subjects.

24. Completing appropriate actions at Research Project completion.

## 10.3 Investigator Concerns

PIs who have concerns or suggestions regarding the VANEOHS human research protection program should convey them to the IRB Co-Chairperson, ACOS/R&D, or COS regarding the issue, when appropriate. In addition, the IRB Administrator will be available to address investigators' questions, concerns and suggestions. If the gravity of the issue is such that it warrants further review, the investigator will be invited to the R&D Committee and/or the IRB meeting for formal committee review.

# Chapter 11 Education and Credentialing for Employees Involved in Human Subjects Research

## 11.1 Purpose

The following describes the procedures for education and credentialing or otherwise validating the qualifications of employees involved in human subjects research activities at the VANEOHS.

VHA employees involved in human subjects research, regardless of appointment mechanism, (Title 38, Title 5, or WOC), must possess adequate credentials and training to ensure their understanding of the protection of human subjects and the ethical conduct of research.

It is critical for the VANEOHS HRPP to ensure there is appropriate training and authorization of all Investigators and their staff who are involved in human subjects research, and that training is on-going.

## 11.2 Definitions

**Human Subject Protection (HSP) Credentialing.** HSP credentialing is the formal systematic process of verifying, screening, and evaluating qualifications and other credentials that include formal (required) education, licensure, registration, certification, relevant training and experience, and current competence.

**Human Subject Protection (HSP) Education.** HSP education requirements include training on the protection of human research.

**Study Staff:** Study staff include: PIs, Co-Is, Study Coordinators and other study staff who interact with subjects in person and/or on the telephone and those who collect and analyze individually identifiable data. This applies regardless of pay status, appointment type, and length of time in the VA facility and includes research staff with a WOC appointment. Study staff who do not have a VA paid appointment must receive a VA Without Compensation (WOC) appointment.

**Research Scope of Practice Statement.** A Research Scope of Practice statement is a written document that defines the parameters and functions of an employee's research duties and responsibilities. These duties and responsibilities must be consistent with the occupational category under which they are hired (appointed by HRM to the position) allowed by license, registration or certification they hold, consistent with their qualifications (education and training) and be agreed upon by the person's immediate supervisor and the Associate Chief of Staff for Research and Development (ACOS/R&D&D). When the employee is working on more than one research study, only one approved Scope of Practice is required as long as it covers all research duties performed.

## 11.3 Responsibilities

The **R&D Committee Coordinator** will ensure that all protocols submitted for review will be reviewed for compliance with credentialing, education, and training prior to submission

to the committees for review

The **ACOS/R&D** is responsible for implementing this policy and providing educational opportunities for the Medical Research Service. The ACOS/R&D is responsible for ensuring that individuals involved in human subjects research have appropriate VA appointments, have been credentialed or had their qualifications validated, and that licenses of individuals in positions requiring a license are verified as current through VetPro, and have a Research Scope of Practice that is consistent with their education, licensure, or certification.

The **ACOS/R&D** is responsible for ensuring that individuals involved in human subjects research receive appropriate initial and on-going training in the ethical principles for human subjects research.

The **ACOS/R&D** will recommend or take disciplinary action against employees who fail to comply with the provisions of this policy.

The **PI** is responsible for ensuring that all individuals involved in the research activity are in compliance with credentialing and training requirements in accordance with this policy. All employees under his/her supervision involved in human subjects research must 1) complete the required credentialing process, 2) have designated functions described in the research scope of practice statement that are consistent with the employee's qualifications, 3) ensure that employees are working within their research scope of practice, and 4) have appropriate VA appointments. The PI is responsible for reviewing the research scope of practice statement on an annual basis.

**PIs** involved in human subjects research are responsible for ensuring that all employees under their supervision, working on approved human subjects research, have completed required training in the ethical principles and acceptable human subjects research practices.

**Study staff** involved in Human Subjects Research are responsible for 1) knowing and adhering to and not practicing beyond the research scope of practice or clinical privileges that have been approved for them, 2) engaging only in human subjects research activities that have been approved as required by VA regulations and policies, 3) completing required training in the ethical principles and acceptable human subjects research practices.

The **Medical Research Service Credentialing Coordinator (RSCC)** is responsible for providing management of the documentation and processing of individual employees including 1) initiation of VA appointments, 2) Maintaining Electronic and/or paper files for all appointees; and 3) Maintaining Research Scopes of Practice in Administrative Files.

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## 11.4 Mandatory Training

All R&D members, IRB members and all staff involved in human subjects research are responsible for learning about, and remaining current on, ethical, legal and regulatory issues related to the conduct of research involving human subjects.

All research staff listed on a human subjects research study must complete a web-based formal education course as determined by the VA ORD. New staff will complete the course PRIOR to performing any duties related to the research study. All others will complete the course every three years, based on a personal training year.

Training exceptions include secretaries; non-human subject research office staff; MCD; and facility-wide committee members, such as the Radiation Safety Committee. Clinical service providers are not required to complete VA research human subjects training.

## 11.5 Credentialing Requirements:

Any study staff who perform independent clinical activities (judgment based independent of the research protocol) as part of their research activities will be allowed to conduct such activities only if they are credentialed and privileged to provide those activities on patients through VetPro. If a clinician would require credentialing through VetPro to perform their activities on patients in a non-research, clinical capacity, VetPro must credential them for purposes of research, and their license status should have been confirmed within the past year. Licenses or certificates that need to be renewed must be confirmed annually.

## Chapter 12 Health Insurance Portability and Accountability Act (HIPAA)

## 12.1 Purpose

The following describe the procedures for conducting research at the VANEOHS in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. NOTE: There are five other statutes that govern the collection, maintenance, and release of information from Veterans Health Administration (VHA) records.

## 12.2 Scope

Public Law 93-579, enacted December 31, 1974, and the HIPAA of 1996 assures that personal information about individuals maintained by federal agencies is limited to that which is legally authorized and necessary and is maintained in a manner which precludes unwarranted intrusion upon privacy. A primary source of regulation in research is the Common Rule. The HIPAA Privacy Rule became effective on April 14, 2003. The Privacy Rule does not make any changes to the Common Rule. However, it does contain several provisions that resemble provisions of the Common Rule and does make reference to those provisions. The Common Rule contains specific requirements for a composition of an IRB and the Privacy Rule contains specific requirements for a Privacy Board. The composition of a Privacy Board is similar to that of an IRB. Even though the IRB is not a replacement for a Privacy Board, the VANEOHS IRB will act as the Privacy Board on behalf of human subjects enrolled in research conducted under the auspices of the VANEOHS. See medical center policy 136-049 “Privacy Policy” for more information.

## 12.3 Definitions

**Access**: The obtaining or using of information, electronically, on paper or other medium, for the purpose of performing an official function.

**Covered Entity**: The VHA is a single covered entity for the purpose of complying with the Privacy Rule. This covered entity includes all VHA hospitals and health care systems.

**De-Identified Information**: Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual.

**Designated Record Set**: A group of records maintained by or for VHA that are the medical records and billing records; enrollment, payment, claims, adjudication and case or medical management records; or used, in whole or part, to make decisions regarding individuals.

**Disclosure**: The release, transfer, provision of access to, or divulging in any other manner outside VHA.
**Health Information**: Any information created or received by a health care provider or health plan that relates to the past, present or future physical or mental health or

condition of an individual; the provision of health care to an individual; or payment for the provision of health care to the individual. This encompasses information pertaining to examination, medical history, diagnosis, findings or treatment, including such information as laboratory examinations, x-rays, microscopic slides, photographs, prescriptions, etc.

**Individually-Identifiable Health Information**: A subset of health information, including demographic information collected from an individual, that is: (1) created or received by a health care provider, health plan or health care clearinghouse; (2.) relates to the past, present or future condition of an individual and provision or payment for health care; and (3.) identifies the individual or a reasonable basis exists to believe that information can be used to identify the individual.

**Limited Data Set**: Protected health information that excludes specific direct identifiers of the individual or of relatives, employers or household members of the individual.

**Privacy Board**: A board composed of members with varying backgrounds and appropriate professional competencies, as necessary, to review the effect of a research protocol on an individual's privacy rights. The IRB will serve as the Privacy Board for human subjects research at the LSDCVAMC.

**Protected Health Information (PHI)**: Individually-identifiable health information that is transmitted or maintained in any form or medium that falls under the Privacy Rule.

**Use**: The sharing, employment, application, utilization or examination of information within VHA.

## 12.4 Responsibilities

The **VANEOHS Privacy Officer** is responsible for facility-wide implementation, coordination and administration of the Act at all campuses. The Privacy Officer will ensure that training is available for all staff on accessing PHI.

The **IRB** is the review board to act upon requests for waivers or alterations of authorization for the use and disclosure of protected health information for human subjects research.

**The PI is** responsible for:

1. Adhering to the policies and procedures set forth in this policy.
2. Adhering to the assurances signed and agreed to with any research review form.
3. Ensuring the confidentiality and protection of any VHA protected health information that is created, accessed, used, and/or disclosed as part of a research project conducted at the VANEOHS.
4. Ensuring that any VHA patient protected health information is not disclosed to any other person or entity, except as required by law or research oversight, or as deemed acceptable by the IRB.

**Study Staff** are responsible for:

1. Adhering to the policies and procedures set forth in this policy.
2. Adhering to the assurances signed and agreed to with any Research Review form.
3. Ensuring the confidentiality and protection of any VHA protected health information that is created, accessed, used, and/or disclosed as part of a research project conducted at the VANEOHS.
4. Ensuring that any VHA patient protected health information is not disclosed to any other person or entity, except as required by law or research oversight, or as deemed acceptable by the IRB.

## 12.5 Human Subjects Research Privacy Policy

1. PIs may only use and/or disclose PHI for research purposes with individual authorization or with a waiver or alteration of authorization, or under other limited circumstances, as set forth in the Privacy Rule.

2. The IRB will serve as the review board to act upon requests for waivers or alterations of authorization for the use and disclosure of protected health information for human subjects research.

3. A research subject has the right to revoke, in writing, his or her authorization at any time by writing to the facility Privacy Officer or Principal Investigator. The individual's revocation is effective, except to the extent that the researcher has taken action in reliance upon the authorization prior to the revocation. The reliance exception permits the continued use and disclosure of PHI already obtained with an authorization to the extent necessary to protect the integrity of the research (e.g., to account for a subject's withdrawal from a study, to conduct investigations of scientific misconduct or to report adverse events).

4. A research subject has the right to access his/her own PHI maintained in a designated record set by completing a "Release of Information Authorization," VA Form 10-5345. An individual's right of access, however, may be suspended during a clinical trial while the research is in progress if, in consenting to participate in research including treatment, the individual agreed to the temporary denial of access. The individual's right to access will be restored upon conclusion of the study.

5. A research subject has the right to receive an accounting of disclosures of PHI made for research purposes in the six years preceding the request, unless the disclosure was made pursuant to a Freedom of Information Act (FOIA) requests part of a limited data set under a data use agreement or was prior to the compliance date. PIs should consult with the Privacy Officer for methods to account for disclosures.

## 12.6 Procedures

1. **Use and Disclosure with Authorization of the Subject**. A PI may use or disclose PHI for research purposes after obtaining authorization from the individual who is the subject of the information.

The written HIPAA authorization may either be a standalone document or combined with the research informed consent approved by the IRB. If a standalone document is used as the written HIPAA authorization, VA Form 10-0493: Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research.

The IRB and PO will conduct an administrative review of the authorization to ensure that the information listed is consistent with the information that appears in the IRB approved study. The IRB and PO reviewed authorization will be dated and signed by the PO. The marked copy is sent to the PI and it is this marked copy that is to be used.

If at any time the study is revised to include the use and/or disclosure of additional information, a revised authorization form is to be submitted for IRB and PO review.

2. **Waiver or Alteration of Authorization.** A PI may use or disclose protected health information for research purposes pursuant to a HIPAA waiver or alteration of authorization.

The PI may request a waiver or alteration of authorization by completing and submitting the form “Request for Waiver or Alteration of Authorization to use and/or Disclose Protected Health Information in Research” to the IRB for review.

3. **De-identification.** PIs may use or disclose health information that is de-identified without restriction. The PI must have the PO certify that the PHI has been de-identified

Re-identification. PI may assign a code, or other means of record identification, in order to allow de-identified information to be re-identified by VHA, provided that

i. The code or other means of record identification is not derived from, or related to, information about the individual and that the code is not otherwise capable of being translated so as to identify the individual;
ii. The code, or other means of re-identification, is not used or disclosed by VHA for any other purpose, and;
iii. VHA does not disclose the mechanism (e.g. algorithm or other tool) for re-identification.
iv. The code must be maintained separate from the research files and the code or mechanism used must not be recorded on identifiable research data (e.g. subject survey).

4. **Limited Data Set.** A PI may use and/or disclose PHI included in a limited data set, pursuant to a data use agreement.

a. A limited data set excludes all direct identifiers listed in paragraph 4C(1) of this policy, with the exception of city, state and Zip Code, all elements of dates and other numbers, characteristics, or codes not listed as direct identifiers.

b. The use of a limited data set requires a data use agreement. This document is intended to provide assurance of the limited use or disclosure of the information in the limited data set.

c. VHA Data Use Forms are available on VHA Forms Intranet at http://vaww.va.gov/vaforms/ (Department of Veterans Affairs Form 10-0403, Responsible Requestor and Project Information Sheet; VA Form 10-0403a, Data Use Agreement; VA Form 10-0403b, Data Access List).

## 12.7 Exceptions

1. **Preparatory to Research:**

Data repositories (including VA medical records) may be used (i.e., accessed) by VA investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization from the subject or waiver of HIPAA authorization by an IRB or Privacy Board. This includes use of PHI for the preparation of a research protocol prior to submission to the IRB(s). “Preparatory to research” activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or Privacy Board, or approval by the IRB(s). This access is granted only to VHA researchers. Non-VHA researchers may not access VHA data for reviews preparatory to research. Additionally, the following holds true:

a. **Representations by the Investigator**. The investigator must make the representations necessary for preparatory access as required by the HIPAA Privacy Rule and document it in the investigator's research files. The representations required by the HIPAA Privacy Rule are:

(1) The access to PHI is only to prepare a protocol. Preparatory to research within VA ends upon the submission of a protocol for review.

(2) No PHI will be removed from the covered entity (i.e., VHA); and

(3) The PHI accessed is necessary for preparation of the research proposed.

b. **Aggregate Data**. Only aggregate data may be recorded in the researcher’s files, and these aggregate data may be used only for background information, to justify the research, or to show that there are adequate numbers of potential subjects to allow the investigator to meet enrollment targets or sample size requirements.

c. **No Recording of Individually Identifiable Health Information**. Individually identifiable health information may not be recorded.

d. **No Recruiting From Data**. Data or information reviewed may not be used for contacting or recruiting subjects.

**e. Repository Requirements**. Investigators must comply with all other access requirements set by the repository of interest.

f. **Agreements**. See VHA Handbook 1200.12 regarding requirements for Data Use Agreements (DUA) or Data Transfer Agreements (DTA).

2. **Research on Decedents' Protected Health.** To use or disclose PHI of the deceased for research, excluding 7332 protected information, VHA PI are not required to obtain authorization from the personal representative or next of kin, a waiver of authorization or a data use agreement. The PI must submit to the Privacy Officer, in writing, certification that:

a. The use or disclosure is sought solely for research on the PHI of decedents.
b. The PHI for which use or disclosure is sought is necessary for research purposes.
c. Documentation may be requested of the death of the individuals whose PHI is sought.
d. Title 38 U.S.C 7332 protected information may be disclosed without a written authorization, if in addition to the above criteria, the requirements of 38 CFR 1.488 are met. Specifically, the research protocol must indicate;
    i. The information must be maintained in accordance with security requirements of 38 CFR Section 1.466;
    ii. The information will not be re-disclosed, except back to the VA; and
    iii. The information will not identify any individual patient in any report of the research, or otherwise disclose patient identities.

3. **Other Uses and Disclosures of PHI.** PI may use or disclose PHI without an authorization, a waiver of authorization or a data use agreement, in other limited circumstances, including:

a. To the extent the use or disclosure is required by law and complies with, and is limited to, the relevant requirements of such law.
b. For disclosure to a public health authority that is authorized by law to collect or receive the information for purposes of preventing or controlling disease, injury or disability. For example, an investigator may disclose PHI related to an adverse event to the NIH or FDA as public health authorities without Authorization.
c. To a person subject to the jurisdiction of the FDA with respect to an FDA regulated product or activity for which the person has responsibility, for purposes related to the quality, safety or effectiveness of the FDA-regulated product or activity.
d. To health oversight agencies for oversight activities authorized by law.

# Chapter 13 Sponsored Research

## 13.1 Purpose

It is VANEOHS policy that any sponsored research conducted under the auspices of the Organization is conducted in accordance with federal guidelines and ethical standards.

The following describe the procedures required to ensure that any sponsored research conducted at the VANEOHS is conducted in accordance with federal guidelines, ethical standards, a fully executed Cooperative Research and Development Agreement (CRADA/agreement) and a study related protocol provided by the sponsor.

## 13.2 Definitions

**Sponsor.** Sponsor means the company, institution, individual donor, or organization responsible for the initiation, management or financing of a research study.

**Sponsored research.** Sponsored research means research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value (data) to the sponsor, in exchange for funding. This may include clinical trials involving investigational drugs, devices or biologics.

**The Cleveland VA Research and Education Foundation (Foundation).** The Foundation is a non-profit flexible funding mechanism established pursuant to PL 100-322 and 38 USC 7361-7368, et seq., and as such facilitates approved VAMC research. The Foundation facilitates the conduct of the studies described below, which have been approved by the VANEOHS R&D Committee and IRB, and shall use all reasonable efforts to ensure performance of the CRADA/agreements. PL 100-322 and 38 USC 7361-7368

## 13.3 Responsibility

The Foundation uses the VA Clinical Trial Cooperative Research and Development Agreement (CRADA) contract with each sponsor which details the organizations' willingness to work together. The CRADA or agreement is negotiated and executed before initiation of the research study; and an executed copy is kept on file at all times with the Foundation. The IRB and the Foundation will share CRADA and study information as necessary for each sponsored protocol to ensure that protocol, consent, and CRADA language are consistent.

The CRADA/agreement includes the following:

1. Agreement that the research will be submitted to the IRB and that the research shall be done in strict accordance with the IRB-approved protocol.
2. Agreement that the sponsor shall be responsible for reasonable and customary costs incurred for treatment of physical injury to the subject if sponsor reasonably determines, after consulting with VANEOHS, that an adverse event was reasonably related to administration of the test article or protocol procedure.

a. Arrangements for medical care for research-related injuries will be provided by the VANEOHS to research participants who are enrolled in a research study approved by the VANEOHS R&D Committee and IRB.

b. If the VANEOHS is not capable of furnishing economical care or is not capable of furnishing the care and services required; the medical center Director shall contract for the needed care. If inpatient care must be provided to a non-veteran under 38 CFR sect. 17.85(b) (1), the medical facility director may contract for such care.

3. Agreement that the sponsor and VANEOHS shall immediately notify each other upon identifying any aspect of the protocol, including information discovered during site monitoring visits, or the study results that may: 1) adversely affect the safety, well-being, or medical care of participants, 2) affect the willingness of participants to continue participation in the research, 3) influence the conduct of the study, or 4) alter the IRB's approval to continue the study. The VANEOHS shall promptly notify the IRB of any such events. When participant safety or medical care could be directly affected by study results, the VANEOHS will send study participants a written communication about these results.
4. Agreement that VANEOHS and the sponsor have the right to make publicly available the results of their research and development activities and are encouraged to do so. The CRADA describe the publication requirements.
5. Statement that if the sponsor monitors the conduct of the research and uncovers information that could affect the safety of participants or their willingness to continue participation, or influence the conduct of the study, or alter the IRB's approval to continue the study, it will assure that the information is communicated immediately to the IRB.
6. A study related budget from the Sponsor is required for presentation to the R&D Committee.

## 13.4 Research and Education

VANEOHS emphasizes that presentation of research results to the scientific community is an essential part of its research programs and that PIs are encouraged to publish and present the results from sponsored research at scientific and medical.

The VA retains ownership of all research data and results obtained from the use of resources provided by the VA as a result of conducting the research pursuant to federal law (35 U.S.C. §§ 102 & 200-212, 37 C.F.R. Part 501, and 38 C.F.R. §§ 1.650-1.663).

## 13.5 Communication of Study Results to Participants

The CRADA specifies that when participant safety or medical care could be directly affected by study results, the VANEOHS and/or the PI, will send study participants a written communication, reviewed and approved by the IRB, about the results.

## 13.6 Addressing Concerns of Research Participants

VANEOHS and the Foundation ensures that all personnel reviewing, conducting, or supporting human research demonstrate and maintain sufficient knowledge of the ethical principles and federal, state, and local requirements for protecting research participants and appropriate processes to respond to their concerns. They ensure that all research participants have access to reliable channels of communication by which concerns are voiced, questions asked, and complaints are addressed.

**Chapter 14** Complaints

## 14.1 Purpose

As part of its commitment to protecting the rights and welfare of human subjects in research, VANEOHS reviews all complaints and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

The following procedures describe how complaints, are handled by the IRB.

## 14.2 Procedures

All complaints involving research subjects must be reported to the R&D Office. The AO/R&D will be the responsible representative for assisting research subjects with questions and/or difficulties that they may have in their relationship with any study staff or protocol within the VANEOHS, and in exercising their rights, and for providing a specific channel through which they can seek resolution of problems, concerns, and unmet needs. The AO/R&D in conjunction with the IRB Administrator will conduct inquiries regarding services provided for the research subject at the VANEOHS. They will have the authority to: 1) review complaints with investigators, 2) review study related records, 3) conduct interviews, and 4) have access to top medical center leadership in order to resolve or ameliorate concerns and enhance the subject's satisfaction and perception of the research program of the VANEOHS. The presentation of a complaint or suggestion does not affect the subject's future access to care nor shall any subject who presents such issues be subjected to any kind reprisal, restraint, interference, coercion or discrimination.

The VANEOHS has a medical center Patient Advocacy Program outlined in medical center policy # 000-008. The Patient Advocacy Program ensures that all veterans and their families who are served at the VANEOHS have their complaints addressed in a convenient and timely manner. The Patient Advocate is available to resolve patients concerns about any aspect of their health care experience that cannot be resolved at the point of care. The Patient Advocate may assist with intake of complaints from research subjects or work with the AO/R&D and IRB Administrator concerning complaints from research subjects. The Patient Advocate will have the authority to review disputes, and cross-departmental lines; he/she will have access to the top medical center leadership.

## Chapter 15 Abbreviations

| | |
|---|---|
| **ACOS/R&D** | Associate Chief of Staff for Research |
| **ADE** | Adverse Device Effect |
| **ADP** | Automated Data Processing |
| **AE** | Adverse Event |
| **AO/R&D** | Administrative Officer for Research (AO/R&D). |
| **APA** | American Psychiatric Association |
| **Case** | Case Western Reserve University |
| **CFR** | Code of Federal Regulations |
| **Co-I** | Co-Investigator |
| **CoC** | Certificate of Confidentiality |
| **COI** | Conflict of Interest |
| **COIC** | Case Conflict of Interest Committee |
| **COS** | Chief of Staff |
| **CPRS** | Computerized Patient Record System |
| **CRADA** | Cooperative Research and Development Agreement |
| **CRADO** | Chief Research and Development Officer |
| **CREC** | Case Continuing Research Education Credit |
| **CSP** | VA Cooperative Studies Program |
| **CSPCC** | CSP Coordinating Center |
| **CTAA** | Cooperative Technology Administration Agreements |
| **DHHS** | Department of Health and Human Services |
| **DOD** | Department of Defense |
| **DPAHC** | Durable Power of Attorney for Health Care |
| **DSMB** | Data Safety Monitoring Board |
| **EOC** | Environment of Care |
| **ePROMISe** | Enterprise Project Management Information System |
| **FAQs** | Frequently Asked Questions |
| **FDA** | Food and Drug Administration |
| **FHPP** | Facility Human Protection Program |
| **Foundation** | Cleveland VA Research and Education Foundation |
| **FTCA** | Federal Tort Claims Act |
| **FWA** | Federal Wide Assurance |
| **GAO** | Government Accountability Office |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HIV** | Human Immunodeficiency Virus |
| **HRMS** | Human Resources Management Services |
| **HRPP** | Human Research Protection Program |
| **HSP** | Human Subject Protection |
| **HUD** | Humanitarian Use Device |
| **IAC** | Case IRB Advisory Committee |
| **IACUC** | Institutional Animal Care and Use Committee |
| **IBC** | Institutional Biosafety Committee |
| **ICF** | Informed Consent Form |
| **IDE** | Investigational Device Exemption |
| **IND** | Investigational New Drug |

| | |
|---|---|
| **IO** | Institutional Official |
| **IP** | Intellectual Property |
| **IPA** | Intergovernmental Personnel Act |
| **IRB** | Institutional Review Board |
| **ISSO** | Information Systems Security Officer |
| **LEIE** | List of Excluded Individuals and Entities |
| **LEP** | Limited English Proficiency |
| **LIP** | Licensed Independent Practitioner |
| **VANEOHS** | Louis Stokes Cleveland VA Medical Center |
| **MEC** | Medical Executive Committee |
| **MOU** | Memorandum of Understanding |
| **NIH** | National Institutes of Health |
| **NSR** | Non-Significant Risk |
| **OGC** | Office of General Counsel |
| **OHRP** | Office for Human Research Protections |
| **OIG** | Office of the Inspector General |
| **ORI** | Office of Research Integrity |
| **ORD** | Office of Research and Development |
| **ORO** | VA Office of Research Oversight |
| **PCAS** | Patient Care Administrative Staff |
| **P&T** | Pharmacy and Therapeutics |
| **PHI** | Protected Health Information |
| **PI** | Principal Investigator |
| **RAC** | Recombinant DNA Advisory Committee |
| **RCC** | Research Credentialing Coordinator |
| **R&D** | Research and Development |
| **R&D C** | Research & Development Committee Coordinator |
| **RCO** | Research Compliance Officer |
| **RCC** | Research Credentialing Coordinator |
| **RCVL** | Resident Credentialing Verification Letter |
| **RIO** | Research Integrity Officer |
| **RIRM** | Research Information Resource Manager |
| **RRRP** | Request to Review a Research Proposal |
| **RSC** | Research Safety Coordinator |
| **RSO** | Radiation Safety Officer |
| **RSSP** | Research Safety and Security Program |
| **SAE** | Serious Adverse Event |
| **SMART** | Site Monitoring and Review Team |
| **SMI** | Serious Mental Illness |
| **SOPs** | Standard Operating Procedures |
| **SR** | Significant Risk |
| **SRS** | Subcommittee on Research Safety |
| **TTP** | Technology Transfer Program |
| **UAE** | Unexpected Adverse Event |
| **URL** | Universal Resource Locators |
| **USC** | United States Code |

| | |
|---|---|
| **VACO** | VA Central Office |
| **VetPro** | VHA's National Electronic Credentials Databank |
| **VHA** | Veterans Health Administration |
| **WOC** | Without Compensation |